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HUMAN CONJUNCTIVITIS DUE TO NEWCASTLE VIRUS IN THE U. S. A.

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Received for publication November 29, 1948

Despite the world wide distribution of Newcastle disease of fowls (1), proved infection of man with this virus has been reported only in Australia (2, 3), and presumed infection of man only in Palestine (6) and, recently, the United States (6). The proved cases of human conjunctivitis due to Newcastle virus here reported establish the pathogenicity of American strains for man, and indicate the liklihood, in the face of broad dissemination of the virus among American flocks (7), of the existence of such infections among our human population.

Three proved cases were reported among Burnet's laboratory workers in Australia. The first (2) developed one day after splashing of infected fluid in the eyes. There occurred a severe, unilateral conjunctivitis and preauricular adenitis, with transitory chills, headache, and malaise. Three days after onset, mild irritation in the other eye was seen. Smears and cultures were negative. The condition cleared in a week. Two later cases (3) presented bilateral and unilateral conjunctivitis, with no systemic symptoms. The author states that in neither of the latter cases was a significant rise in antibody titer demonstrated by serum neutralization of virus hemagglutination. In all cases, Newcastle virus was isolated by inoculation of chick embryos with acute-phase eyewashings.

In Palestine, 17 kitchen workers were afflicted with unilateral conjunctivitis and preauricular adenitis 3 to 4 days after preparing infected poultry (4). A technician who contaminated her eye with Newcastle infected material developed a sub-conjunctival hemorrhage, but no conjunctivitis (5). Neither of these Palestine reports includes virus isolation or serologic studies.

Howitt, et al. (6), have reported from Tennessee the discovery of rises in antibody titer to Newcastle virus in paired sera from children who suffered an unexplained febrile illness. This was characterized by

fever, headache, and malaise, being accompanied sometimes by nausea, vomiting and signs of meningeal irritation, and persisting at most for a few days. High antibody titers were seen, too, in isolated serum samples from these patients, whereas none appeared in a control group. Many of the children had contact with chickens. A number of laboratory workers exposed to Newcastle virus showed similar rises after an influenza-like illness. No cases of conjunctivitis were reported.

CASE REPORTS

Case 1. L. D., handled Newcastle virus contaminated laboratory refuse the day before onset of marked conjunctivitis in the right eye. The right preauricular node became palpable and tender. This condition cleared slowly over 5 days. On the third day, there appeared on the left an acute conjunctivitis and preauricular adenitis which also cleared in 5 days. There was no exposure to contaminated material after onset of the right-sided infection.

Isolation of Newcastle virus from the right eye was successful on the first day and unsuccessful on the second and fourth days of infection. One day after onset of the infection in the left eye, virus was isolated from this eye. Saline eye washings were penicillin-treated and inoculated on the chorio-allantoic membranes of 10 to 12 day chick embryos. Both positive washings killed 3 embryos in 3 days. Allantoic fluids from these eggs agglutinated red cells in a dilution of at least 1/2560. Newcastle-immune chicken serum in a dilution of 1/100 inhibited hemagglutination by 10 agglutinating doses of the virus. Normal chicken serum, beyond a 1/2 dilution, failed to do so.

TABLE 1

Serological studies on L. D.

DAY AFTER ONSET SERUM TAKEN	SERUM DILUTION NEUTRALIZING VIRUS HEMAGGLUTINATION	SERUM DILUTION AGGLUTINATING VIRUS-SENSITIZED RED CELLS	EMBRYO DEATHS WITH 10^{-7} VIRUS + SERUM DILUTIONS:			
			Undil.	1/4	1/16	1/64
0	None with undil. serum	1/640	4/4	3/3	4/4	2/4
1	None with undil. serum	1/320				
3	None with undil. serum	1/640				
6	None with undil. serum	1/320				
14	None with undil. serum	1/160	0/4	1/4	2/4	2/3
22		1/320				

Case 2. M. F., having harvested infected allantoic fluid the previous day, developed a unilateral, moderately severe follicular conjunctivitis accompanied by

profuse watery discharge and slight preauricular node enlargement. The condition cleared in 4 days. Scrapings and bacterial cultures were negative.

First and second day eye washings killed chick embryos in 2 days. Hemagglutination titers of fluids from these eggs rose from 1/20 and 1/40 to 1/5120 and 1/320, respectively on second egg passage. The virus was isolated and identified with the same methods as in Case 1. Intramuscular injection of passage I of the first day eye washings into 2 normal chickens caused their deaths in 4 days.

TABLE 2

Serological studies on M. F.

DAY AFTER ONSET SERUM TAKEN	SERUM DILUTION NEUTRALIZING VIRUS-HEMAGGLUTINATION	SERUM DILUTION AGGLUTINATING VIRUS-SENSITIZED RED CELLS	EMBRYO DEATHS WITH 10^{-7} VIRUS + SERUM DILUTIONS:			
			Undil.	1/4	1/16	1/64
0	1/40	1/20				
2	1/80	1/20				
5	1/160	1/80		0/3	2/3	4/4
142	1/80	1/40		1/3	2/3	4/4

Case 3. J. C., worked daily with Newcastle virus in the laboratory. She developed moderate, unilateral conjunctival infection and palpebral swellings. The preauricular node was palpable and tender. Her illness subsided after 6 days.

Isolation of virus was attempted unsuccessfully from eye washings taken on the fourth day of the disease.

TABLE 3

Serological studies on J. C.

DAY AFTER ONSET SERUM TAKEN	SERUM DILUTION NEUTRALIZING VIRUS-HEMAGGLUTINATION	SERUM DILUTION AGGLUTINATING VIRUS-SENSITIZED RED CELLS	EMBRYO DEATHS WITH 10^{-7} VIRUS + SERUM DILUTIONS:			
			Undil.	1/4	1/16	1/64
3	1/40	0	3/3	3/3	4/4	
10	1/80	1/20	1/3	4/4	4/4	
17	1/80	1/10	2/4	4/4	4/4	

METHODS

All dilutions were made in buffered saline. Washed, human, type "O" red blood cells, in 1 per cent suspension in buffered saline, were used in agglutination tests.

Neutralization of hemagglutination was tested by adding 0.5 cc. of serum dilutions to 0.5 cc. of virus (10 hemagglutinating doses), letting stand at room temperature for 30 minutes, then adding 1 cc. of red cell suspension and reading agglutination patterns after 1 hour.

Sensitized red blood cells (a washed 1 per cent suspension of cells previously exposed in an incubator to Newcastle virus and by this rendered inagglutinable by the virus) (10) were added in 0.5 cc. amounts to 0.5 cc. of serum dilutions, and the tubes read after 1 hour at 4°C. in Case 1, at 20°C. in cases 2 and

Neutralization of virus infectivity was tested by adding equal volumes of serum dilutions and a 10^{-7} virus dilution (about 10 LD_{50}'s). One drop of the mixture was inoculated on the chorio-allantoic membrane of 10 to 12 day embryos. The end point was determined by deaths occurring between 1 and 6 days. All serum was frozen at −16 shortly after separation from the clot, and was tested immediately after thawing. Acute and convalescent sera were tested simultaneously.

Strains B and CG 179 of Newcastle virus are used in this laboratory (8).

DISCUSSION

Clinically, these patients presented an acute, unilateral or bilateral conjunctivitis and preauricular lymphadenitis. The course was brief and without complication, no systemic symptoms were observed. Several other laboratory workers exposed to the virus have developed no illness.

Repeated tests on the sera of these patients reveal a very low antibody response to infection. This and the fact that we had to use a minimal amount of virus (10 L.M.D.) and undiluted sera to demonstrate this rise, suggest that serologic diagnosis of this conjunctivitis may require exceptionally complete studies in order to be significant. Isolation of the virus in the early stage of the disease, when possible, is to be preferred for ease and accuracy.

The slight antibody response may be related to localization of the infection on the conjunctival epithelium. (It is interesting to note that in trachoma and inclusion conjunctivitis, also superficial conjunctival virus infection, there has been found no evidence of specific serological response (9).) On the other hand, Howitt et al. (6), present data suggesting that systemic infection with Newcastle virus may stimulate high antibody levels.

Sera from some patients with infectious mononucleosis and other infectious diseases (10, 11) have been found to agglutinate Newcastle virus sensitized red blood cells to a high titer (though not to neutralize Newcastle virus hemagglutination, differentiating them from Newcastle-immune sera). The possibility of a relationship between the causative agents of the diseases has been suggested (10). Sera from

these known human Newcastle infections failed to present similar high titers of sensitized-cell agglutinins.

SUMMARY

1. The virus of Newcastle disease in chickens in the United States is capable of causing conjunctivitis in man, as demonstrated by the accidental infection of three laboratory workers. Virus was isolated from 2 of the cases.

2. Serologic studies indicate that antibody response is slight in these cases, and that laboratory diagnosis in these superficial infections should rest on isolation of the virus.

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TREMOR AND CHANGES IN REFLEX STATUS PRODUCED BY DDT IN DECEREBRATE, DECEREBRATE-DECEREBELLATE AND SPINAL ANIMALS[1]

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In the intact mammal DDT (2,2-bis-parachlorophenyl-1,1,1-trichloroethane) produces muscle tremors, dysmetria and hypermetria during walking, exaggerated standing (strong positive supporting reaction) and often an inability to arrest forward progression (1, 8). In both acute and chronic poisoning tonic and clonic convulsions may occur. Since several of these disturbances are ones which characterize the decerebellate animal it has been suggested (1, 5) that in DDT intoxication the cerebellum is selectively affected. An electroencephalographic study of the central effects of DDT in cats and monkeys, carried out by Crescitelli and Gilman (3), showed notable changes in two areas, the region of the motor cortex and certain portions of the cerebellar cortex. In curarized, unanesthetized animals fast waves, completely synchronized in these areas, increased in magnitude and frequency until periodic electrical seizures, corresponding apparently to the the tonic-clonic convulsions seen in non-curarized animals, developed. It was concluded that either of the two regions "was firing into the other or both were being simultaneously driven by a group of neurones linked to both." The most definite claim that DDT acts selectively on the cerebellum has been made by Haymaker, Ginzler and Ferguson (5) who found degenerative changes restricted to the cerebellum (chiefly in the dentate and roof nuclei) when they studied sections of the cord and brain from dogs that had been chronically poisoned by relatively large doses of DDT. Other neurohistological studies either failed to demonstrate any abnormalities attributable to the poison (7) or revealed only slight or moderate degenerations in cord (2) or in cord and brain stem (6).

[1] This work was done under contract between the Medical Division of the Chemical Warfare Service and The Johns Hopkins University.

On the basis of the clinical symptoms produced by DDT, the electroencephalographic data of Crescitelli and Gilman and their own pathological studies, Haymaker, Ginzler and Ferguson (5) state that "it appears that the cerebellum is the chief portion of the nervous system on which DDT acts." They refer to unpublished work (p. 429) in which it was found that after transection of the spinal cord in cats DDT failed to produce tremors in muscles innervated from the isolated cord. They also refer to acute experiments in which low mesencephalic truncation of the brain stem failed to interrupt the "neurological symptoms" (presumably the tremor) of DDT poisoning.

In some preliminary experiments we noted that in spinal cats typical DDT tremors occurred in muscles innervated from below the level of transection, and a little later we found that in the decerebrate cat complete removal of the cerebellum had little or no effect on the tremors produced in such preparations by DDT. These observations suggested that DDT may act quite generally on the central nervous system and led to the work described below in which special attention was devoted to the tremor and to the alterations in reflex status which are induced by DDT.

METHODS

The animals used in this investigation were cats and dogs. A number were surviving (chronic) preparations which were studied some weeks or months after surgical exclusion of one or another part of the central nervous system, or transection of the spinal cord. In a larger number of instances we employed acute preparations, animals in which such procedures as decerebration or decerebration combined with spinal section or removal of the cerebellum were carried out shortly before or after administration of DDT. Observations of the animal then extended over a period of some hours.

In the case of the chronic preparations the operations were carried out with rigorous aseptic precautions and under deep pentobarbital sodium anesthesia (42 mg. per Kg. body weight, intraperitoneally). In the acute preparations all operative procedures were done under brief but deep ether anesthesia, the rapid recovery from which permitted the central effects of previously administered DDT to show themselves within a short time. We repeatedly observed that in decerebrate animals all overt neurological signs of the intoxication quickly disappear with very light etherization and that on withdrawal of ether after deep anesthetization the symptoms reappear with surprising rapidity.

DDT was administered in two ways. In all experiments on long surviving animals and in one-half of the acute experiments it was administered by stomach

tube in the form of a 10 per cent solution in peanut oil. In a half of the acute experiments it was administered intravenously in an emulsion prepared by the method described by Phillips and Gilman (8). As pointed out by these authors the intravenous method has the advantage that the symptoms develop more rapidly and the response to a given dose is much more regular than when the substance is administered orally (intragastrically). It was found, however, that in decerebrate cats the intravenous administration of the emulsion always produced immediate signs of a central disturbance. Sometimes a bilateral or a unilateral facial paralysis was produced. In those cases in which this was permanent it masked the development of the first signs of intoxication, namely, twitching of the eyelids and face. Also, when the emulsions were used in decerebrate cats the survival times were very much shorter than when the substance was given intragastrically. These untoward effects occurred in spite of great care to use emulsions only immediately after homogenization or re-homogenization and to keep the rate of injection low. Further, it was found that the intravenous injection of the emulsion without DDT, in a volume corresponding to the usual dose per kilogram of body weight, produced not only these same effects but also an extremely fine, very rapid and widely distributed muscular fibrillation which was maintained throughout survivals of several hours. Although this activity was easily distinguishable from the finer components of the tremor evoked by DDT, we not unnaturally concluded that despite certain disadvantages the administration of DDT by stomach tube is the procedure of choice.

Others (8) have noted that the response to the oral (or intragastric) administration of DDT is somewhat capricious and that symptoms appear after considerable delay. In our experience the latency, with doses of from 100 to 400 mg. per Kg., varied from 2 to 14 hours, but it did not seem to be related closely to the dosage. On the other hand, doses of 60 mg. per Kg., when administered intravenously, caused typical symptoms to appear in from 5 to 35 minutes (average, 19.6 minutes). Accordingly, in the case of acute experiments, when the intravenous route was used, the first operative procedure on the central nervous system was carried out before giving DDT, whereas when the substance was administered by stomach tube the first procedure followed the giving of DDT and was usually performed just after the first signs of an effect appeared.

EXPERIMENTAL RESULTS

1. *Normal Animals*

In order the better to appraise the effects of operative procedures on the development and course of the neuromuscular phenomena produced by DDT a series of normal, wholly intact cats and dogs were given the substance by the intragastric route. In no case did we attempt to produce the chronic state of intoxication described by Bing, McNamara and Hopkins (1). The symptoms which our animals de-

veloped were essentially the same as those described by Phillips and Gilman (8). Typically there appeared, first, rapidly repeated blinking of the eyelids, then fine twitchings of the vibrissae and ears. Next, the activity spread caudally to involve, usually *seriatim*, the muscles of the neck, shoulder girdle, forelegs, hips, hindlegs and trunk. Not infrequently the tail showed tremors and twitches earlier than did hips, hindlegs and lumbar region. In most cases a very fine tremor developed first and persisted, but later a more gross activity, perhaps adequately described as rapidly repeated synchronous "jerkings" of muscle masses, was superimposed on the fine tremor. When the intoxication was sufficient these "jerkings" or "shakes" became tonic-clonic convulsions.

2. *Decerebrate Cats (Acute Experiments)*

The effects of DDT were examined successfully in 14 cats which were subjected to removal of all cerebral tissue rostral to transections of the brain stem made at various levels between the middle of the mesencephalon and the upper portions of the pontile region. No differences in symptoms produced by DDT were noted which could be attributed to differences in the level of decerebration.

In 7 of these 14 experiments DDT was given intravenously after decerebration and development of the rigidity and the reflex status characteristic of such preparations. The intervals between decerebration and injection ranged from 22 to 146 minutes (average, 61 minutes). In each case the dose was 60 mg. per Kg. In every instance the injection was accompanied by one or more temporary but conspicuous disturbances (opisthotonus, abrupt increase or decrease in rigidity, apnea, gasping, hyperpnea, polypnea, facial paralysis, nystagmus, retching); in two animals a complete facial paralysis lasted throughout the experiment. Following these immediate and, for the most part, temporary changes each of the animals presented in general the features of the typical decerebrate cat. After receiving the injection six of this group remained in good condition for periods which varied from 55 to 129 minutes (average, 96 minutes). One cat died ten minutes after completion of the injection, but before its exitus it developed a typical DDT tremor. Four were subjected to other operations (decerebellation or cord section) after receiving DDT, but there is good evidence

that these procedures had little influence on the survival times (see below). Two succumbed immediately after receiving a second intravenous injection of the emulsion. When these survival times are compared with those of the decerebrate cats which received DDT by stomach tube, it becomes evident that intravenous injections of an emulsion containing DDT greately curtailed the lives of such preparations.

Decerebration was carried out in 7 other animals which received DDT, dissolved in peanut oil, intragastrically. In one of these the operation was done 4.5 hours before DDT was given. In all others of this series decerebration was performed after administration of DDT, the intervals being 3 hours and 18 minutes (3:18), 4:35, 5:00, 1:40, 2:05 and 1:10. Except in the case of the two shortest intervals, nervous symptoms of DDT poisoning appeared before the operation with its attendant etherization was begun. Although in 5 of these animals other operative procedures (decerebellation or cord section) were carried out subsequent to decerebration, the animals survived for the following periods of time: 24 hours and 15 minutes (24:15); 32:05; 00:39; 23:10; 29:30; 7:30; and 18:55. Four were killed intentionally, one (survival, 7.5 hours) after a severe clonic fit; two died; and one, the animal which survived decerebration only 39 minutes, succumbed in the course of an attempt to remove the cerebellum. On the basis of a rather extensive experience in preparing, and studying for the longest possible time, bulbospinal and midbrain cats, it would appear that moderate poisoning with DDT (when it is administered intragastrically) tends to prolong the life of the decerebrate animal!

Each of the 14 cats comprising the two groups of decerebrates just described clearly showed the tremor characteristic of intact cats poisoned with DDT. As in intact cats it typically began (except when facial paralysis supervened after intravenous administration) in the facial region. In several cases, when the effects of the poison were not great, the tremor occurred spontaneously only in the foreparts, especially the face, neck and shoulder girdle. When this state of affairs existed, the tremor could be induced in the hindparts reflexly by slight manipulation of the entire animal or by gentle handling of a hindleg or the tail. With augmentation and caudal spread of the activity two components, one a fine tremor or fasciculation, the other a more gross

and jerky movement, could be distinguished. Occasionally, especially when the tremor and the twitchings were very vigorous, a convulsive seizure, either clonic or tonic or both, intervened.

It is evident that the most outstanding and most constant feature of DDT intoxication seen in the cat with central nervous system intact, the characteristic tremor, can be evoked by this substance in animals from which all cerebral tissue in front of the hindbrain has been removed. Since the acute bulbospinal cat cannot right itself, stand by itself or walk, these experiments do not answer the question whether the several disorders of stance and locomotion seen in intact poisoned animals are due to interference with forebrain mechanisms or cerebellar-forebrain relationships. These experiments, however, do demonstrate conclusively that DDT exerts profound effects on parts of the neuraxis situated caudad to the mesencephalon and that those effects result in neuromuscular activity which resembles very closely—in fact is indistinguishable from—that evoked by DDT in the animal without any surgical ablation of central nervous tissue.

Evidence was also obtained in these experiments that DDT causes several peculiar changes in the neurological status of the bulbospinal cat. In almost every animal, with the development of tremor and sometimes before any tremor appeared, the forepaws, spontaneously or in response to some slight stimulus of the paw, were strongly flexed and the claws protruded. This occurred when the hindlegs were showing strong extensor rigidity and so produced an attitude which was in strong contrast to that seen in the unpoisoned decerebrate preparation. Another commonly observed response, one rarely if every evocable in "normal" decerebrate cats, was a bilateral or crossed knee-jerk. On tapping one patellar tendon phasic extension occurred at both knee joints and usually the crossed response was as great as the ipsilateral. While the tonic neck and labyrinthine reflexes seemed unaffected (possibly they were sometimes enhanced), an additional effect of lateral flexion of the head, one we have never been able to evoke in an unpoisoned bulbospinal cat, was almost always encountered—deviation of the tail to the jaw side. This reaction may be called the *ipsilateral head-tail response*. Not infrequently the poisoned decerebrate cats gave the impression of a somewhat generalized increase in reflex excitability, especially of the extensor responses. In a few animals slight

pressure against the toe pads evoked strong extension of the leg. The augmentation of the tremors and twitchings by slight tactile or proprioceptive stimuli was suggestive of a strychnine-like effect. In one animal clapping the hands increased the intensity of the tremor.

3. *The Effect of Removal of the Cerebellum in the Acutely Decerebrate Cat*

In 5 cats of the decerebrate series just described ablation of the cerebellum (in each case by gentle suction) was carried out either immediately after decerebration (cats 4 and 18) or after an interval during which symptoms of intoxication were in evidence (cats 2, 3 and 19).

Three of these animals were given DDT intravenously (cats 2, 3 and 4) and were observed under the influence of the poison for relatively short periods of time (48, 43 and 152 minutes, respectively) while in the decerebrate-decerebellate condition. In cat 2 the tremors which had developed in the decerebrate state remained generalized and showed no decrease in vigor; there was some slight increase in the gross jerkings, but this could have been due to the further development of the intoxication. In cat 3 the fine component, the only one present before removal of the cerebellum, largely disappeared and was replaced by a coarse tremor which was maintained until the animal died during a second intravenous injection of the DDT emulsion. Cat 4, subjected to decerebellation immediately after decerebration, developed vigorous generalized tremors and "shakes." At first the grosser component seemed unusually conspicuous, but later there was a marked increment in the fine component.

The two animals of this group, cats 18 and 19, which received DDT by stomach tube were observed in the decerebrate-decerebellate condition for 28.8 and 3.7 hours, respectively. Cat 18 had been given DDT (160 mg. per Kg.) 100 minutes before completion of the removals, but had failed to exhibit any symptoms over an observation period of more than 11 hours. Another dose, equal to the first, was administered during the twelfth postoperative hour and the first signs of an effect (presumably chiefly due to the first dose) developed about an hour later. Both a fine and a gross tremor appeared in head and tail. For a long time it occurred elsewhere only in response to han-

dling the animal. Toward the end of the experiment spontaneous gross tremors in the axial muscles were combined with fine tremors in the distal portions of the extremities; both were augmented by any slight mechanical disturbance of the animal. On the basis of other experiments it is apparent that no very considerable quantity of the DDT administered reached its sites of action on the nervous system. Cat 19 was decerebrated after the beginning of blepharospasm. During the following three hours it developed very vigorous tremors in all parts of the body and strong gross twitching was superimposed on the fine tremor. Twenty minutes after completion of the decerebellation and withdrawal of ether vigorous twitches were apparent in eyelids, face, neck and tail. Fifteen minutes later almost the entire skeletal musculature showed both the fine tremor and the gross twitching. The twitches became more and more vigorous and finally, 3 hours and 40 minutes after decerebellation (7.5 hours after decerebration), the animal went into a convulsion which began with running movements and developed into violent clonic movements of the entire body attended by piloerection.

The evidence provided by these experiments indicates that the neurological symptoms produced in the decerebrate cat by DDT are not essentially modified by removal of the cerebellum. As indicated above, there may have been some tendency for the gross twitching to be somewhat more marked than in the simple decerebrate preparation, but of this one cannot be sure; the grosser aspects of the DDT tremor usually increase with increasing intoxication and this could have been the cause of the gross twitches noted in cats 2, 3 and 19.

The peculiar changes in reflex status produced in decerebrate cats by DDT and noted above were also seen in the poisoned decerebrate-decerebellate animals.

The development of a convulsive episode in cat 19, which was quite like those seen in intact cats after large doses of DDT, is of special interest, for it suggests that in the intact animal neither cerebrum nor cerebellum is essential for this feature of DDT intoxication. It is very possible indeed that had other cats of this series received larger doses of DDT they too would have developed convulsions; several had fits of running movements.

4. *An Observation on a Chronically Decerebellate Dog*

That the presence of the cerebellum is not essential for the occurrence of a DDT convulsion was further demonstrated by an experiment carried out on a dog twenty-three months after complete removal of his cerebellum. During this long postoperative period the animal had been studied intensively in the course of another investigation. He had remained in excellent health and exhibited all the characteristics shown by dogs after uncomplicated extirpation of the cerebellum. At 4:15 p.m. the animal was given DDT dissolved in peanut oil in a dose amounting to 200 mg. per Kg. of body weight. At 6:30 no symptoms had appeared and the animal was left unobserved. At 8:30 (4.25 hours after DDT) the dog was found panting heavily and noisily and shaking so violently that the loud rattling of the cage attracted attention in a far part of the building. On removing the animal from its cage it at once fell onto its side, rolled over, urinated, and went into a tonic convulsion with all limbs flexed and back deeply concave. Death occurred in two or three minutes. It is unfortunate that the observation was so brief, but it was clear enough that the animal had developed a violent attack of DDT "shakes" which culminated in a tonic convulsion.

5. *Spinal Animals*

A. *Acute Experiments on Cats.* In 4 cats of the decerebrate series decerebration was followed by transection of the spinal cord at a thoracic level. After this procedure the muscles of the pelvic girdle, hindlegs, and tail were innervated from an isolated cord, while the innervation of the foreparts remained "decerebrate." A comparison of the motor activities of the two portions of the body permitted some judgment of the susceptibility of spinal mechanisms, freed from all supraspinal influences, to the action of DDT.

Cat 4 was given DDT intravenously (60 mg. per Kg.) after decerebration and decerebellation. Seventy-two minutes later, when very vigorous generalized tremors had developed, the cord was transected between the 11th and 12th thoracic segments. Five minutes after withdrawal of the ether a fine tremor was present in hindlegs and tail. Seventeen minutes later the tremor was as marked in hindlegs as in

forelegs. Before the animal died during a second intravenous injection of DDT there was a marked increase in the vigor of the tremors and twitches of parts innervated from above and from below the transection. Throughout the occurrence of tremor in the parts innervated by the isolated cord the knee-jerks were bilateral (crossed) and the hindlegs assumed an attitude of flexion and markedly resisted passive extension. In cat 5 the cord was cut at the same thoracic level twenty-five minutes after decerebration and thirty-three minutes before DDT was given intravenously (60 mg. per Kg.). Fifteen minutes after the injection small tremors began simultaneously in all four legs. During the rest of the period of survival (the cat died 95 minutes after the injection) both ends of the cat showed typical tremors and in each part they became more vigorous when that part was manipulated.[2]

In two cats (Nos. 12 and 15), which had received DDT by the intragastric route and were showing good tremors and twitches throughout the body after decerebration, the spinal cord was transected at a mid- or high thoracic level (in cat 12 at T6, in cat 15 at T3). Of these cat 12 showed the greater effect, doubtless because it was given a larger amount of DDT: 200 mg. per Kg. initially and 400 mg. per Kg. just after section of the cord. During the first six hours following the transection there was a slow but steady increase in the spontaneous tremors and twitches of all muscles innervated from parts of the neuraxis lying above the section, but tremors appeared in the hindparts only reflexly. A very slight passive movement of one hindlimb sufficed to induce kicking movements of both hindlegs and, in all parts innervated from below the section, vigorous tremors which were somewhat more gross than those occurring spontaneously in the foreparts. During this same time there developed other signs of an altered reflex status of the isolated cord. The knee-jerks were bilateral and the

[2] It should be stated here that in cat 5, as in several other preparations which were showing typical DDT tremors in hindlegs and tail, the femoral and sciatic nerves were cut on one side and the caudal segments of the spinal cord removed. These procedures put an end to all tremors in the tail and in the limb muscles whose innervation was thus interrupted. Such observations, however, do not prove that in the mammal DDT has little or no peripheral action. Indeed we have recently learned of evidence that the substance has a veratrinic action on nerve and on curarized muscle (4).

hindlegs, kept in a semi-flexed position, strongly resisted passive extension. These alterations in cord activity remained throughout the survival of the preparation. A tremor appeared spontaneously in the tail 6.25 hours after cord section. At this time the head and forelegs had long been showing gross jerks superimposed on a fine tremor. Within the next three hours the hindlegs began to show spontaneous tremorous activity, but while this was qualitatively the same as that going on in the foreparts it was not as vigorous. This picture was maintained for approximately 7.5 hours. During this time the isolated cord developed an extraordinary reflex excitability which is never seen in the ordinary acute or semi-chronic spinal preparation. The hindlegs showed ipsilateral and crossed knee-jerks, a good mark-time reflex, the lengthening reaction and its crossed component (Philippson's reflex) and the tonic flexion mentioned above. The flexion reflex of each hindleg acquired an amazingly low threshold; a light touch applied between the toes evoked strong withdrawal of the foot. During the last five hours of this cat's survival there was a gradual regression of the changes produced by the DDT; the spontaneous tremor weakened in the foreparts and disappeared in the hindparts where, however, it could still be induced by manipulation of tail or of a hindleg. Finally, tremors could be induced only reflexly in the foreparts.

In cat 15 the same procedures were carried out as in cat 12, and in the same sequence. It received an initial dose of 160 mg. per Kg. and a second dose of the same amount just before the cord was transected. Following the transection this animal displayed very much the same activity as did cat 12. In hindlegs and tail the tremors occurred spontaneously, but they never became as vigorous as in the foreparts.

B. *Chronic Spinal Preparations.* Although the results described above leave no doubt that DDT can act on the isolated spinal cord to produce tremor and changes in reflex status and threshold, it seemed desirable to test the effects of the substance in animals which had long survived a transection of the cord. This was done in two cats and two dogs.

Cat A3 was given DDT (160 mg. per Kg.) by stomach tube 69 days after transection of the cord at the second thoracic segment. After 2.3 hours a slight tremor appeared in the foreparts when the

animal was moved. It was not until 6 hours had elapsed that blepharospasm and a tremor in the forelegs occurred spontaneously. At this time the knee-jerks became crossed (bilateral), probably the first indication of an effect upon the isolated cord. An hour later a rather gross tremor was present in the foreparts and tremors appeared in hindlegs and tail when one or the other was manipulated. For another hour the tremors remained spontaneous in the head and forelegs, only reflexly elicitable in tail and hindlegs.

Cat A5 showed a more pronounced effect of the same amount of DDT (160 mg. per Kg.). The experiment was done 37 days after transection of the cord between the third and fourth thoracic segments. Definitely characteristic DDT tremors appeared spontaneously in hindparts and foreparts 2.5 hours after the substance was given by stomach tube. In the hindlegs the tremors were less continuous and not as fine as in the forelegs. The tail was now showing marked gross twitches. During the next 2.5 hours the activity became greater in all parts, but the same difference was maintained between the normally innervated and the spinally innervated regions. Early in the sixth hour the animal had a convulsion and died. Just before this episode the hindlegs and tail exhibited strong gross tremors. They did not take part in the convulsive activity.

Dog A received DDT (150 mg. per Kg., intragastrically) at 3:40 p.m. on the fifteenth day after transection of the cord between T10 and T11. A slight tremor appeared in the foreparts at 5:50 and during the next hour gradually increased in vigor. Blepharospasm was present, but not continuous and not very strong. Aside from an augmentation of the knee-jerks, which became "decerebrate" in type, the hindparts showed no evidence of any effect until 7:00 when the hindlegs began to show a definite tremor. At 8:00 the dog became excited, vocalized, was unable to right the shoulder girdle and executed some running movements with the forelegs. Then the part of the body above the transection developed a tonic spasm with forelegs rigidly extended, head thrust forward, jaws open and mouth frothing During this seizure vigorous tremors occurred in face and forelegs. While the hindparts did not take part in the fit, they showed tremors which were entirely unrelated in phase or intensity to the activities which occurred in the foreparts. At 8:15 the rectal temperature was 41.5° C.

and enough pentobarbital sodium was given to produce relaxation. By 8:30 the animal was entirely quiet and relaxed except for a fine tremor in the foreparts. When she had recovered from the effects of the barbiturate twelve hours later no trace of tremor was observable in any part of the body.

In a second dog (No. SD1) the cord was transected at a mid-thoracic level and the effects of DDT were tested on five occasions between the 13th and the 27th postoperative days. The initial dose varied from 150 to 250 mg. per Kg. and in one test was twice repeated. In two of these five experiments, with single doses of 200 mg. per Kg., the effects produced were so slight that they need not be considered here. On the first test, begun on the 13th day, 150 mg. per Kg. were given. A tremor of high frequency and small amplitude appeared during the seventh hour both in the normally innervated foreparts and in the spinally innervated hindparts. A little later some gross twitching was added to the fine tremor in hindlegs and tail. With this the hindlegs showed increased extension. The tremor disappeared after the twenty-fourth hour. Three days later, when 200 mg. per Kg. were given, tremors appeared in all parts of the body after three hours, became maximal after seven hours and then decreased until, during the twenty-third hour, they were present only in the foreparts. In the muscles innervated from the isolated cord the tremors were never as rapid, vigorous or continuous as those occurring concurrently in the foreparts. A second dose of 200 mg. per Kg. was given 22.3 hours after the first, and within two hours the tremor reappeared in the hindparts. It was as strong and as fine in character, but not as continuous, as that in the foreparts and it continued for more than five hours. At the end of the thirteenth hour tremor was absent from the foreparts, but a very slight one could be made out in the hindlegs. This unusual situation still prevailed after 26.5 hours; a discontinuous fine tremor was still evident in the hindlegs, but no tremor of any kind was observable in the foreparts. At this time (it was the 19th postoperative day) a third dose of 200 mg. per Kg. was administered and gave rise to a very marked continuous tremor in head, shoulders and forelegs and a somewhat less vigorous and slightly intermittent one in the hindlegs and tail, both of which effects persisted for many hours.

Finally, on the 26th day, 250 mg. per Kg. led to a continuous very strong tremor in all parts of the body musculature. Gradually, over a period of 8.5 hours, this activity diminished until only the forelegs showed a slight tremor, the hindparts having become quiescent some time before.

In two of the tests carried out on dog SD1 oscillographic records of the electrical activities of foreleg and hindleg muscles were taken from small wire electrodes, insulated down to their tips, which were thrust into a flexor or extensor muscle. These records indicated that, except for some intermittency and some deficiency in frequency, the tremorous contractions of groups of fibers in hindleg muscles were qualitatively the same as those in muscles of the forelegs. On comparison with records taken when the animal was not under the influence of DDT, they also gave evidence of an action of the poison on the reflex status of the isolated cord, an action which was also evident on simple visual observation of the reflexes. This consisted in signs of increased extensor tonus, augmentation of knee-jerks and the reflex of crossed extension with an enormous prolongation of after-discharge. Even the knee-jerks showed after-discharge. In the electrical records the after-discharge of the crossed-extension reflex, evoked by pinching the foot of the opposite hindleg, was found to last as long as 1.5 minutes. In the case of the knee-jerk the electrical activity of the responding muscles showed that muscle units fired repetitively for many seconds after the initial discharge. On visual observation the leg showed corresponding clonic extensions. Thus it appears that DDT acts on the isolated cord of the dog not only to produce tremors, but also to bring about a reflex status which resembles that of the decerebrate condition.

SUMMARY AND CONCLUSIONS

1. In acutely decerebrate cats DDT produces a tremor which is indistinguishable from that induced in normal animals by the poison. It also causes signs of an altered central state or "set of the center," which is indicated by: a tendency of forepaws to be flexed with claws protruded; crossed (bilateral) knee-jerks; appearance of the "ipsilateral head-tail response;" and some increase in reflex excitability, especially of extensor responses.

2. The effects produced by DDT in the decerebrate cat are not essentially modified by removal of the cerebellum. In the decerebrate-decerebellate cat DDT may evoke a tonic-clonic convulsion. A seizure of this type was seen in a dog which was given DDT twenty-three months after total uncomplicated ablation of the cerebellum.

3. While these experiments demonstrate that forebrain, mesencepahalon and cerebellum are in no way necessary for the development of the tremor characteristic of the intact animal poisoned by DDT, they do not permit any conclusion as to the site or sites of the action of this substance which results in abnormalities of stance and locomotion in the animal with central nervous system intact.

4. DDT produces tremor in muscles innervated from segments of the spinal cord which have been deprived of all neural connections with the brain. This fact has been shown in animals with cord transected at a thoracic level and studied either in the chronic spinal state or in the acute decerebrate condition. When such animals are given DDT the tremor usually appears first in the foreparts. When the intoxication is light, as judged by the behavior of the foreparts, the tremor may appear only reflexly in the hindparts in response to a mechanical disturbance of that portion of the body. With deeper levels of poisoning, tremor occurs spontaneously in the hindparts, but may not attain the vigor of the activity present in muscles innervated from above the transection. Sometimes, but by no means invariably, the tremor in the muscles innervated from the isolated cord is not as fine as that in the foreparts, the coarse component being more prominent.

5. DDT acts to alter the reflex activities of the isolated lumbosacral cord. In the case of the cat there is augmentation of flexor tone, lowering of threshold of the flexion reflex, and irradiation of impulses from proprioceptors of the knee extensors to give a crossed knee-jerk. In the spinal dog the reflexes involving hindleg extensor muscles become more active and show very long after-discharges.

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A CONSTANT DEGREE OF ANOXEMIA OBTAINED BY THE ADMINISTRATION OF A GAS OF VARIABLE OXYGEN CONCENTRATION[1]

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INTRODUCTION

In a previous report a method of producing a constant degree of anoxemia was described (1). It consisted of altering the oxygen concentration of the inspired gas mixture as necessary to give the desired degree of arterial oxygen saturation, as measured by the oximeter. The inspired gases were administered by means of an anesthesia machine containing tanks of pure oxygen and pure nitrogen.

It was noted at that time that frequent changes in the flow rate of oxygen and nitrogen were necessary to maintain the arterial oxygen saturation at 85, 80 or 75%. It is the purpose of this communication to present data obtained by gasometric analysis of the inspired gas during such controlled anoxemia tests and to described modifications of and further experiences with the controlled anoxemia technique, with especial reference to the comparison of this procedure with the administration of a low oxygen gas of constant concentration.

METHOD

All subjects were young adults on whom a previous physical examination and electrocardiogram were found to be normal. The method of inducing and maintaining the desired level of anoxemia was essentially the same as that described in the earlier report, save that a mouthpiece and nose clip replaced the O.E.M. mask. The anesthesia machine and tubing were tested to detect any possible leakage from the outside air. In the experiments in which a gas with constant oxygen percentage (10.7% O_2) was used, the tank containing this gas replaced the nitrogen in the anesthesia machine. The subject rested for ap-

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proximately 30 minutes until the blood pressure and pulse reached resting levels (available from previous studies done on the same subject). During this period, the oximeter earpiece was attached to the subject's ear and "ear thickness" readings were taken to determine when vasodilatation was complete. Figure 1 illustrates the apparatus described above in use during an actual experiment.

FIG. 1

Samples of the inspired gas were taken only after the arterial oxygen saturation had been constant, at the desired percentage, for at least $1\frac{1}{2}$ minutes. The samples were taken into Bailey bottles (2) from a tube connecting the inflow tube of the gas machine to the breathing bag. Each sample was then passed through a drying column of calcium sulphate to a Pauling Oxygen Analyzer, Model C, for direct measurement of the oxygen tension. The pO_2 values thus obtained were converted to oxygen percentage. The Pauling apparatus was checked frequently against a Scholander analyser (3) and found to give readings consistently 1–3 mm. higher than obtained with the Scholander.

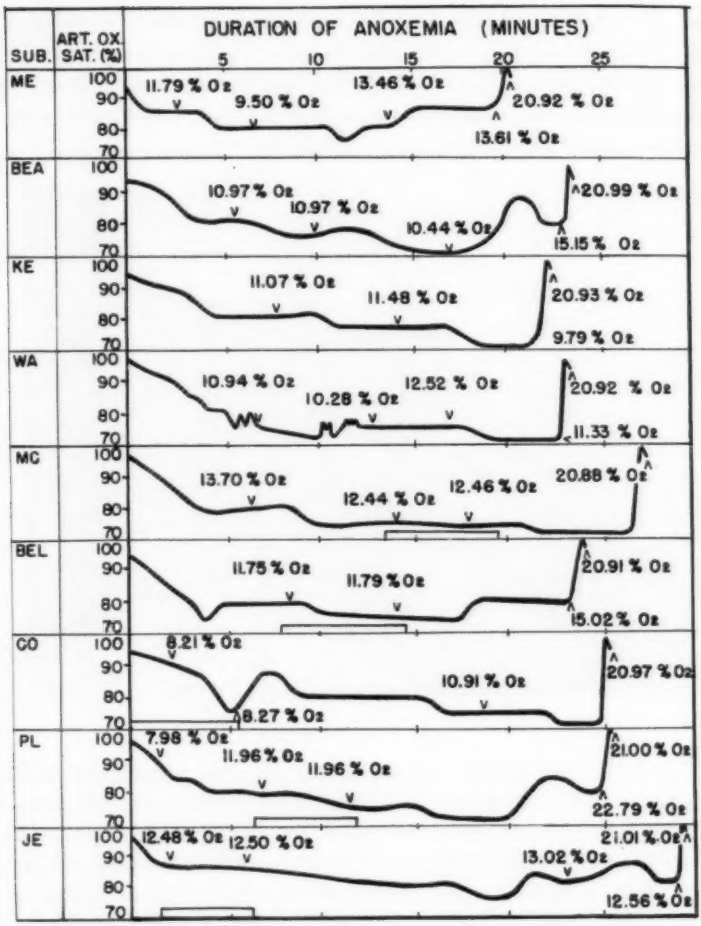

FIG. 2. GRAPHIC ILLUSTRATION OF THE RELATIONSHIP OF THE ARTERIAL OXYGEN SATURATION AND OXYGEN CONCENTRATION OF THE INSPIRED GAS

⌐¬ indicates period during which oxygen and nitrogen flow rates were not changed. V indicates point at which gas sample was taken.

TABLE 1

The Oxygen Concentration of the Inspired Gas with Progressively Decreasing Arterial Oxygen Saturation

SUBJECT	ARTERIAL OXYGEN SATURATION	OXYGEN CONCENTRATION OF INSPIRED GAS
	%	%
Me	85	11.79
	80	9.50
Bea	80	10.97
	75	10.97
	70	10.44
Ke	80	11.07
	75	11.48
	70	9.79
Wa	75–80	10.94
	75	10.28
	70	11.33
Mc	80	13.70
	75	12.44
Bel	80	11.75
	75	11.79
Co	91	8.21
	75	8.27
Pl	90	7.98
	80	11.96
	75	11.96
Je	87	12.50
	80	13.20

RESULTS

The Variability of the Oxygen Concentration of the Inspired Gas with Constant Arterial Oxygen Saturation

A total of 41 oxygen tension analyses was done on 9 subjects. The relationship of the oxygen percentage of the inspired gas to the arterial saturation is graphically presented in Figure 2.

In Table 1 the values of the oxygen concentration obtained at

progressively decreasing arterial oxygen saturations are recorded. The poor correlation of the oxygen concentration and the arterial saturation is striking even in this small group.

In Table 2 analyses of the oxygen percentage of gas samples obtained at the *same* arterial saturation in the *same* individual are compared. In these six instances, the subjects, after being taken to progressively lower levels of arterial saturation were made gradually *less* anoxemic towards the end of the experiment. In this manner two gas analyses could be made at one particular saturation. The widely varying value of the oxygen percentage, even when the arterial saturation is the same, is again striking. It is of interest to note that, in five of the

TABLE 2

The Oxygen Concentration of the Inspired Gas at the Same Arterial Oxygen Saturation
#1 Gas sample was taken *before* #2 at the particular arterial saturation.

SUBJECT	ARTERIAL OXYGEN SATURATION	OXYGEN CONCENTRATION OF INSPIRED GAS	
		#1	#2
	%	%	%
Me	80	9.50	13.46
Bea	80	10.97	15.15
Bel	80	11.75	15.02
Co	75	8.27	10.91
Pl	80	11.96	22.79
Je	80	13.02	12.56

six instances, the oxygen concentration obtained *after* the subject was brought up from the lower level was from *2.6* to *10.8*% higher than the concentration necessary to produce the same degree of anoxemia earlier in the experiment.

In evaluating the gas analysis data, it is appropriate to consider to what extent these data may have been affected by experimental error in gas analysis and in oximetry. To establish the limits of accuracy of the gas analysis the following procedure was carried out with five subjects (Mc, Bel, Co, Pl, and Je in Figure 2): While the oxygen and nitrogen flow rates remained constant, two samples of gas were taken several minutes apart for comparison. The difference in oxygen percentage between the five sets of samples was .02, .04, .06, 0.0 and 0.02%. It, therefore, was felt that errors from this source were insig-

nificant. Error from oximeter "drift" was also relatively small, never exceeding 2½ percentage units.

Stability of the Arterial Oxygen Saturation with Oximeter Controlled Anoxemia

79 anoxemia tests with oximeter control were done on 59 subjects. In the beginning of this series the arterial saturation was lowered to 85% or 80% and kept at this level for the entire anoxemic period (approximately 20 minutes) with the intention of studying the subjects at lower levels on subsequent occasions. It was later decided, however, to induce anoxemia in a "stepwise" manner, i.e., decreasing the saturation to successively lower levels during the same test. When this procedure was used, the subject was usually kept at each level for approximately 5 minutes. The number of tests are given below according to the saturation to which the subject was initially taken, and at which he was subsequently maintained:

NO. OF TESTS	INITIALLY TAKEN TO	MAINTAINED AT
	%	%
4	85	85
19	80	80
31	80	80 and 75
16	80	80, 75 and 70
7	75	75
2	75	75 and 70

In 49 of these 79 tests the subject could be brought to the desired level of saturation within a half minute of the time desired, and be kept within 1% of this level throughout the entire period of anoxemia. In 14 tests the subject usually was within 1–2% of the desired saturation or occasionally deviated by a few percent for a minute. In 10 tests, the saturation fluctuated about 2% from the desired arterial oxygen saturation, swinging regularly around the desired percentage of arterial saturation. With 6 subjects, no stable level of arterial saturation could be induced or maintained on the first test. Four of these 6 subjects had repeat tests, three of which were perfectly stable and the fourth unstable.

The induction and maintenance of a constant, steady arterial oxygen saturation, regardless of level, depended chiefly on the *gradual* induction of anoxemia; 5 minutes were necessary to bring a subject from the normal saturation point of approximately 97% (on room air) down to 80%. It was found that at this rate of induction, the subject could be brought to 80% and kept at a constant level without "overshooting." The changes from 80% to 75%, and from 75% to 70% were carried out in 1½ minutes in order to prevent similar over-shootng and general instability of the degree of saturation.

In general, a particular individual was just as stable at one level as at another. There was also little difference in stability of the test between the first 10 and the second 10 minutes of the test.

In summary, practically all subjects could be induced to levels of 85%, 80%, 75% (and some 70%) saturation and maintained at these levels for the desired length of time.

Variability of the Arterial Oxygen Saturation with Inhalation of Low Oxygen of Constant Concentration

A demonstrative group of experiments illustrating the nature of the variability of the arterial oxygen saturation with inhalation of a constant low O_2 gas is presented in Figure 3. Here a few relaxed subjects, entirely familiar with the procedure, inhaled the 10.7% O_2 for approximately twenty minutes under ideal laboratory conditions. Only one subject (Figure 3a) had two "smooth" tests in both of which his arterial oxygen saturation was approximately the same. Another subject (Figure 3b) had a higher and more unstable saturation in a repeat test showing considerable variation with each respiration. In Figure 3c the arterial saturation of 4 subjects is compared showing a variation not only in the *depth* of saturation attained at the end of the twenty minute period, but also a variation in the *rate* with which the arterial saturation was lowered.

In contrast to this, oximeter control of anoxemia was used on three of these same subjects on other occasions. In every instance it was possible to induce the subject to the desired level of arterial saturation (75%) in a standard length of time (5 minutes) and to keep the saturation within 1–2% of this level throughout the remainder of the test.

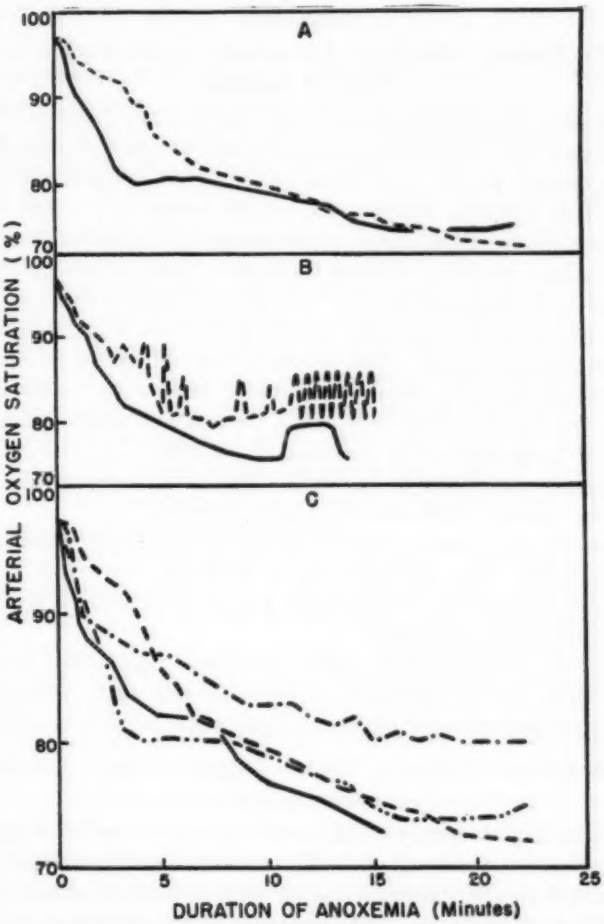

FIG. 3. DIFFERENCES IN THE RESPONSE OF THE ARTERIAL OXYGEN SATURATION WITH INHALATION OF THE SAME LOW OXYGEN GAS (10.7% O_2)

In A, one subject with two relatively similar tests. In B, another subject with two strikingly different tests. In C, the variability of the rate and degree of arterial oxygen "desaturation" with inhalation of 10.7% O_2 by four different subjects.

DISCUSSION

The Relationship of the Oxygen Concentration of the Inspired Gas to the Degree of Anoxemia

The data presented in Figure 1, and Tables 1 and 2, are in complete agreement with Malmström's statement that the oxygen concentration of the inspired air is a "poor index" of the resulting degree of anoxemia (4). This disparity between the oxygen percentage of the inhaled gas and the resulting degree of anoxemia is in agreement with the observations made by Höhwu-Christensen and Krogh (1935). As quoted by Malmström (4), they "examined 50 healthy flyers by letting them rebreathe in a gas tank of 200 liters while simultaneously absorbing carbon dioxide. The test continued till the subjects became so strained that they were not capable of performing qualified work. When the test had to be interrupted, the alveolar oxygen tension was found to be approximately the same (about 30mm Hg) in all subjects. The oxygen percentage in the inspired gas varied a great deal at that moment: between 5.93 and 9.97 volume percent."

From the data given in Table 2 another point of physiologic interest can be made—that the *longer* one is anoxemic, the *higher* must the oxygen concentration of the inhaled gas be to maintain a given level of arterial oxygen saturation.

The chief inference to be drawn from these data is that control of the arterial oxygen saturation in any anoxemia study requires that the oxygen percentage of the inspired gas be altered almost constantly.

The Advantages of Oximeter Control of Arterial Oxygen Saturation in Anoxemia Studies

1. *Control of the Degree of Anoxemia.* Under "Results" it has been shown that practically all of the 59 unselected healthy subjects could be induced to and maintained at the desired level of arterial oxygen saturation. This is the chief advantage of the controlled anoxemia method and can best be appreciated when one considers the variability of the arterial oxygen saturation resulting from the inhalation of a gas of fixed low oxygen concentration. This subject has been extensively reviewed by Malmström (4). The arterial oxygen saturation with inhalation of 8%, 9%, 10% and 12% oxygen, as recorded by various workers, is shown in Table 3. The variability of the satura-

tion is striking throughout, regardless of method or type of subject used.

The importance of being able to control the degree of anoxemia in any anoxemia test, e.g., of cardiac function, has also been mentioned and stressed by Barach and Steiner (5f), Mannheimer (6a), Houston (6b), Malmström (4), Lindgren (5e), Biörck (6c) and Dripps and Comroe (5a). Work done on animals and human beings has emphasized the need for a method of controlling the level of arterial oxygen saturation in studying the many physiological effects of anoxemia. Wiggers (7a) has reported that when the arterial oxygen saturation is lowered from 55% to 35%, a "cardiovascular crisis" supervenes. Hilton and Eichholtz (7b), measuring the coronary blood flow of dogs directly, showed that there was a direct relationship between the arterial oxygen saturation and the rate of coronary blood flow. In human beings, increase in heart rate (5a), activity of the carotid body (8a), visual acuity (8b), and integration of the central nervous system (8c) have been found to have a direct relationship to the degree of arterial oxygen saturation.

2. *Control of the Rate of Induction of Anoxemia.* The work of Malmström clearly shows that in a group of normal subjects inhaling the same low oxygen gas, the rate of arterial oxygen "desaturation", as well as the degree, varies considerably. Administering 9% O_2 to 19 normal subjects, he found the average arterial saturation to be 10.5% lower after 15 minutes than at the end of 5 minutes. The rate of desaturation was quite irregular with the difference between 15 minute and 5 minute values ranging from -22% to $+8\%$. These variations in rate and degree of desaturation are demonstrated even in our own small group of subjects breathing 10.7% O_2 (Figure 3).

The physiologic significance of being able to standardize the rate of induction of anoxemia has been clearly demonstrated in animals (9). Those animals made rapidly anoxemic showed a qualitatively different cardiovascular response from those made gradually anoxemic. Also, rapid induction often produced convulsions. The uncontrolled rate of induction with the administration of a gas of fixed oxygen concentration may well account for the occasional serious nervous symptoms and cardiovascular collapse reported with the 10% O_2 test of cardiac function (10, 6c).

TABLE 3

The Variability of the Arterial Oxygen Saturation with Inhalation of 8%, 9%, 10% and 12% Oxygen

% O_2	AUTHOR	METHOD OF INDUCING ANOXEMIA	METHOD OF MEASURING ARTERIAL OXYGEN SATURATION	TYPE OF SUBJECT	NO. OF SUBJ.	ARTERIAL OXYGEN SATURATION			
						Mean (%)	Std. dev.	Std. err. mean	Range (%)
8	Dripps and Comroe (5a)*	Tank (of low O_2 gas)	Oximeter	Normal	11	72.8	4.9	1.47	64 –79
	Wood and Geraci (5b)	Tank	Blood (Gas Analysis)	Normal	10	62.2			53.6–69.1
	Rahn and Otis (5c)	(High Altitude) Chamber (22,000 ft.)	Oximeter	Normal	8	69.0			
9	Henson et al. (5d)	Chamber (20,000 ft.)	Oximeter	Normal	9	70.8	5.83	2.06	
	Malmstrom§ (4)	Tank	Blood	Normal	29	58.8	9.6	1.78	44 –82
	Rahn and Otis	Chamber (20,000 ft.)	Oximeter	Normal	8	74.0			
10	Dripps and Comroe*	Tank	Oximeter	Normal	34	73.8	6.6	1.15	54 –85
	Henson et al.	Chamber (18,000 ft.)	Oximeter	Normal	13	71.2	6.54	1.89	
	Lindgren (5e)	Tank	Oximeter	Normal	11	71.0			
	Wood and Geraci	Tank	Blood	Normal	9	72.4			66.3–77.8
	Rahn and Otis	Chamber (18,000 ft.)	Oximeter	Normal	8	75.0			
	Barach and Steiner (5f)	Tank	Blood	Normal	8	65.9			52 –78

* Statistical values calculated from the authors' data.

TABLE 3.—*Continued*

% O_2	AUTHOR	METHOD OF INDUCING ANOXEMIA	METHOD OF MEASURING ARTERIAL OXYGEN SATURATION	TYPE OF SUBJECT	NO. OF SUBJ.	ARTERIAL OXYGEN SATURATION			
						Mean (%)	Std. dev.	Std. err. mean	Range (%)
12	Dripps and Comroe*	Tank	Oximeter	Normal	32	80.2	5.6	.99	68 –88
	Henson et al.	Chamber (14,000 ft.)	Oximeter	Normal	17	79.2	4.05	1.01	
	Wood and Geraci	Tank	Blood	Normal	9	79.7			70.4–95.0
10	Barach and Steiner**	Tank	Blood	Cardiac	28	67.6			55 –89
	Lindgren	Tank	Oximeter	Cardiac	13	69			
12	Levy et al. (10)	Tank	Blood	Cardiac	17	70.9			50.1–84.6

** One cardiac patient, whose blood arterial oxygen saturation fell to 34% with inhalation of 10% O_2, was excluded from calculations as the control value was only 76% on room air.

The use of a variable low oxygen gas to induce anoxemia enables us to control the rate with which a subject is taken to the desired level of arterial oxygen saturation. This should, therefore, help standardize the cardiovascular response to anoxemia and avoid some of the nervous symptoms.

3. *Knowledge of Arterial Oxygen Saturation During the Test.* Another definite advantage of any procedure in which the oximeter is used is that the arterial oxygen saturation is known instantly at all times. The importance of avoiding saturations as low as 50% in normal subjects and cardiac patients inhaling fixed low O_2 gases has been mentioned previously (1). Workers using 8%, 10% and even 12% O_2 have reported that in many instances tests had to be terminated before the end of the usual 10 or 20 minute period because of the occurrence of symptoms which could well have been due to an unexpectedly low arterial saturation. With the oximeter one could readily terminate the test if the saturation for any reason took a precipitous drop.

The oximeter also allows us to measure the arterial saturation of a

normal subject even while he is still breathing room air by comparing this saturation with that obtained during the inhalation of pure oxygen (11). This procedure may prevent the inadvertent administration of a low oxygen gas to a subject whose arterial blood is abnormally unsaturated while breathing room air (5f).

SUMMARY

Further experiences with the use of a low oxygen gas of variable concentration to induce a constant degree of anoxemia are presented. The oxygen concentration of the inspired gas was analyzed with a Pauling oxygen analyzer, and it was established that the concentration had to be almost continually altered to induce and maintain the desired arterial oxygen saturation in a small group of normal subjects.

The technique of administering this variable oxygen mixture was used in 79 anoxemia tests in which the subject was lowered to levels of 85, 80, 75 and 70% arterial saturation. Practically all subjects could be induced to these levels at a standardized rate and maintained at the desired level for the remainder of the test.

The advantages of the "controlled anoxemia" technique over the administration of a gas of *fixed* low oxygen concentration are: (1) it controls the degree of anoxemia (2) it controls the rate of induction of anoxemia and (3) the arterial saturation is known instantly throughout the test. The physiologic importance of oxymeter control of anoxemia is discussed.

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THE TREATMENT OF ACUTE BRUCELLOSIS WITH AUREOMYCIN[1,2]

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Despite the advances in chemotherapy of bacterial disease since the introduction of the sulfonamides, penicillin and streptomycin, the treatment of brucella infections has been a therapeutic problem (1). In a preliminary report describing the early clinical trial of aureomycin, a patient ill with brucellosis, who had been successfully treated, was reported (2). Subsequent observation of this patient, together with further experiences with this antibiotic in the treatment of four additional patients, are presented at this time to supplement the earlier report.

IN VITRO STUDIES

The sensitivity to aureomycin *in vitro* of eleven recently isolated strains of *Brucella suis* and *abortus* has been investigated and the results are tabulated in Table 1. Samples of six different lots of aureomycin were tested. The antibiotic, dissolved in 0.85 per cent saline, was added to Trypticase Soy Agar (B.B.L.; pH 7.0) while the latter was still fluid at a temperature of 50°C. Plates were poured immediately and, after cooling, they were inoculated directly with a forty-eight hour broth culture of the test strain.

It will be noted in Table 1 that the six strains of *Brucella suis* were completely inhibited after forty-eight to seventy-two hours of incubation by 0.25 to 0.5 micrograms of aureomycin per milliliter of medium.

[1] The aureomycin used was supplied by the Lederle Laboratories Division, American Cyanamid Company.

[2] These investigations were partially supported by grants received from Abbott Laboratories; Eli Lilly and Company; Lederle Laboratories Division, American Cyanamid Company; Parke, Davis and Company; and the Upjohn Company.

Despite the known instability of this antibiotic (2, 3, 4, 5) in neutral or alkaline media, complete inhibition of growth of relatively heavy inocula was still present after seven days when the concentration of the drug was 2.0 to 4.0 micrograms. Strains of *Brucella abortus* were somewhat more variable in their reaction to aureomycin and were inhibited by 0.25 to 2.0 micrograms per milliliter after forty-eight to seventy-two hours incubation. When observed after seven days incu-

TABLE 1

Sensitivity of Brucella to Aureomycin

STRAIN	TYPE	SOURCE	SENSITIVITY* OF BRUCELLA TO VARIOUS SAMPLES OF AUREOMYCIN IN MICROGRAMS/MILLILITER											
			PERIOD OF INCUBATION											
			48 and 72 hours						7 days					
			1†	2	3	4	5	6	1	2	3	4	5	6
2	Brucella suis	Case #4	0.5	0.5	0.5	1.0	0.5	0.5	2.0	2.0	2.0	4.0	2.0	2.0
5	" "	Case #5	0.5	0.5	0.5	0.5	0.5	0.25	2.0	2.0	2.0	2.0	2.0	2.0
6	" "	Case #3	0.25	0.25	0.25	0.25	0.25	0.25	2.0	2.0	2.0	2.0	2.0	2.0
8	" "	Case #1	0.5	0.5	0.5	0.5	0.5	0.5	2.0	2.0	2.0	2.0	2.0	2.0
9	" "	Human	0.5	0.5	0.5	0.5	0.5	0.25	2.0	2.0	2.0	2.0	2.0	2.0
16	" "	"	0.5	0.5	1.0	1.0	0.5	0.5	4.0	4.0	4.0	4.0	4.0	4.0
1	Brucella abortus	"	1.0	1.0	1.0	1.0	1.0	1.0	4.0	4.0	4.0	4.0	4.0	4.0
7	" "	"	0.5	1.0	0.5	1.0	0.5	1.0	2.0	4.0	4.0	4.0	2.0	4.0
11	" "	"	0.25	0.25	0.25	0.25	0.25	0.25	4.0	4.0	4.0	4.0	4.0	4.0
14	" "	"	1.0	1.0	1.0	1.0	1.0	1.0	4.0	4.0	4.0	4.0	4.0	4.0
19	" "	"	2.0	2.0	2.0	2.0	2.0	2.0	4.0+‡	4.0+	4.0	4.0+	4.0	4.0

* Sensitivity = lowest concentration at which no growth was observed.
‡ + = growth at the highest concentration employed.
† 1 = Lederle Laboratories Lot No. 7-7854
2 = " " " " " 7-8020A
3 = " " " " " 7-8071A
4 = " " " " " 7-8071B
5 = " " " " " 7-8254
6 = " " " " " 7-8411

bation, four of the *Brucella abortus* strains were completely inhibited by 2.0 to 4.0 micrograms of aureomycin per milliliter but one strain was resistant to the latter concentration, which was the highest level tested.

Inasmuch as the strains of brucella were so sensitive to aureomycin, and the response obtained with the first patient was so promising, other patients ill with acute brucellosis were treated. Preliminary observations in experimental animals and humans had shown that the toxicity of this antibiotic was relatively low (2, 6, 7, 8, 9).

CASE PRESENTATIONS

Case #1: P. T., a 45 year old fireman in a local meat processing plant, was hospitalized[3] on February 14, 1948 because of chills and fever of two weeks' duration.

The patient had always been in good health until two weeks before admission when he experienced occipital headache, weakness, chills and fever. Chills occuring in the afternoon continued and, five days before admission, sulfadiazine was prescribed with some diminution in these symptoms. However, feverishness and drenching night sweats persisted. Two days before admission, an agglutination test was reported as significantly positive for brucella antibodies and he was referred to the hospital.

The patient was a well-developed and well-nourished male who was not in acute distress. His temperature was 100°F. and the skin of the upper chest and face was flushed. The heart and lungs were normal. No masses or viscera were palpable on abdominal examination. No petechial or other eruptions were present.

Urinalysis and blood chemical examinations were normal. The hemoglobin was 13.2 grams; the total leukocyte count was 13,200 with a differential of polymorphoneuclearleukocytes, 81 per cent and mononuclear cells, 19 per cent. The corrected sedimentation rate was 41 millimeters (Wintrobe).

Blood cultures were repeatedly and promptly positive for *Brucella suis* in three different laboratories. He was treated with 6 grams of sulfadiazine per day for twenty-three days and 3.0 grams of streptomycin intramuscularly daily for twelve days. Slight symptomatic improvement was noted but blood cultures were repeatedly positive during the period of combined drug therapy and subsequent to its termination. A trial with polymyxin D^{10} was then deemed warranted and he was treated with 7.5 milligrams per kilogram of body weight intramuscularly daily for ten days. During this treatment his blood cultures promptly became negative and remained negative for one month. His general condition improved, although, fever up to 100°F. (R) persisted. The patient was discharged on April 1, 1948 and was followed at weekly intervals.

He was readmitted to the hospital on May 3, 1948 because of recurrence of chills, fever, headache, malaise and night sweats during the preceding week. Blood cultures obtained at weekly intervals had been sterile until April 26, 1948 when *Brucella suis* was again cultured.

On physical examination the patient appeared ill. His temperature was 102°F., pulse 96 per minute and blood pressure 120/80. The skin was flushed, warm and moist. Erythema of the face, neck and upper thorax was marked. Petechial lesions were present on one toe and several fingers. Funduscopic examination showed a white area in the region of the right fovea. This was interpreted by the ophthalmological consultant as a "manifestation of a previous hemorrhage, prob-

[3] Cases #1, 3 and 5 were admitted to Sinai Hospital, Baltimore, Maryland where they were on the service of Dr. Milton Sherry, Physician-in-Chief.

ably of embolic nature." The lungs were normal to percussion and auscultation. The heart was not enlarged but a soft systolic murmur was intermittently audible at the cardiac apex. His liver was enlarged two fingerbreadths below the right costal margin but splenomegaly was not detected. Clubbing of the fingers and toes was present.

The total leukocyte count was 3,200 with a differential of polymorphoneuclear-leukocytes 79 per cent and mononuclear cells 21 per cent; hemoglobin was 13.4 grams. The corrected sedimentation rate was 22 millimeters (Wintrobe). Urinalyses, blood chemical determinations, liver and kidney function tests were normal. Agglutination tests for brucella ranged in titer from 1:5,120 to 1:20,480; for

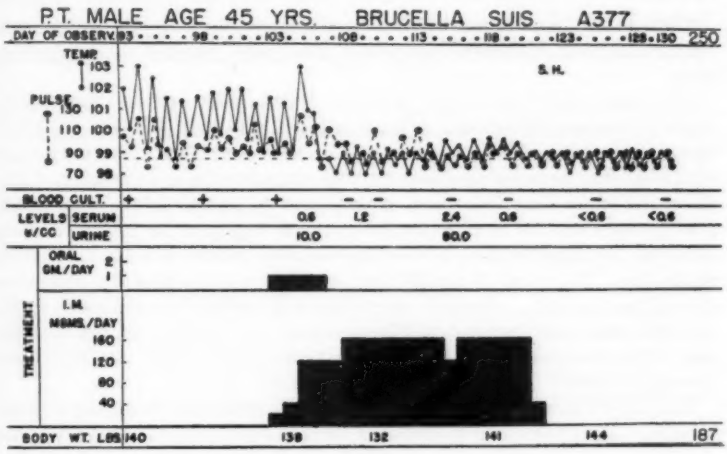

FIG. 1

tularemia the titer was 1:320. Typhoid O and H and paratyphoid A and B agglutination tests were negative. A determination of opsonins for brucella showed a marked increase of phagocytosis in the presence of the patient's serum when compared to that of a normal control.

During the ten days prior to initiating treatment with aureomycin three consecutive blood cultures, positive for *Brucella suis*, were obtained. The last of these cultures was taken immediately before treatment. Since oral preparations of aureomycin were not available, this patient received crude aureomycin (lot No. 205–214) in improvised capsules. A total oral dose of 0.5 gram twice daily was administered for four days. This dose was supplemented by intramuscular aureomycin hydrochloride. Forty milligrams were administered intramuscularly every six hours for approximately twenty days. During this entire period he received a total of 6.7 grams of the antibiotic. Moderate nausea and anorexia were noted

while the patient was receiving oral crude aureomycin. Local tenderness and induration resulted from the intramuscular injections even when they were given in 1 per cent procaine solution.

The patient's temperature became normal within three days after aureomycin therapy was initiated. The liver regressed progressively and no new petechiae or emboli were observed. Eight blood cultures taken during the fifty days of hospitalization, concomitant with and following aureomycin therapy, were sterile. To date, eight months have elapsed since therapy with aureomycin was discontinued. The patient has remained well and has gained forty pounds in weight. He has returned to his former occupation and has performed his duties without difficulty.

Case #2:[4] P. S., a 48 year old farmer, was hospitalized on July 26, 1948 with the complaints of progressive weakness of three years' duration and intermittent fever.

The patient had been in good health until three years ago, at which time he began to complain of weakness and easy fatigability. Associated with this loss of energy, he experienced night sweats and frequent headaches. The fatigue and exhaustion had increased progressively, with exacerbations and remissions during the course of the next three years, accompanied by periodic fevers. One month prior to entry into the hospital, the patient again began to have chilly sensations and fever. An agglutination test for brucellosis was positive in a dilution of 1:320 at this time. He was given penicillin for several days and appeared to show some clinical improvement. However, his fatigue and weakness continued up to the point of complete exhaustion during the next fortnight. Four days prior to admission, his temperature rose to 104°F. and ranged between 102°F.–104°F. until the time of admission.

Past history revealed that the patient had definite contact with Bang's disease in cattle. Three years prior to admission, there had been an outbreak of contagious abortion among his cattle. Despite this he continued to drink raw milk freely.

The patient was a lethargic, disoriented white male who appeared ill. Both his physical and mental reactions seemed unduly sluggish. The temperature was 102°F., pulse 96, respirations 20 and the blood pressure was 100 systolic, 90 diastolic. Except for occasional basilar rales in the posterior lung fields, the physical examination was normal.

His hemoglobin was 15 grams with a hematocrit of 46; his white cell count was 6,000 with 62 per cent neutrophiles, 36 per cent lymphocytes and 2 per cent monocytes. Repeated urinalyses were normal. The sedimentation rate was 38 millimeters per hour. Agglutination tests employing *B. tularensa*, *B. paratyphosa* A and B, *B. typhosa* and *B. proteus* OX_{19} as antigens were all negative. A blood culture taken at the time of admission was positive for gram-negative cocco-bacilli after ten days. These were identified as brucella organisms (abortus) by Dr. Carl

[4] The authors are indebted to Dr. Sidney Ross, Children's Hospital, Washington, D. C. for his observations and the collection of data in this case.

Larson at the National Institute of Health. Agglutination tests for *Brucella abortus* were positive in a dilution of 1:1,280.

On the day following admission, oral therapy with aureomycin was begun. During the first twenty-four hours, the patient received 200 milligrams every two hours. For the following thirteen days the dose was 200 milligrams every four hours. The patient's temperature fell to normal by lysis within seventy-two hours. He remained afebrile during the remainder of his hospital course. Concomitantly, a striking clinical improvement was noted. He began to feel considerably stronger and his sensorium cleared within five days after the initiation of therapy. There was a noteworthy improvement in appetite and vigor, and within ten days after aureomycin treatment had been begun the patient was ambulatory. Following therapy, seven blood cultures were obtained during a twelve day period and all

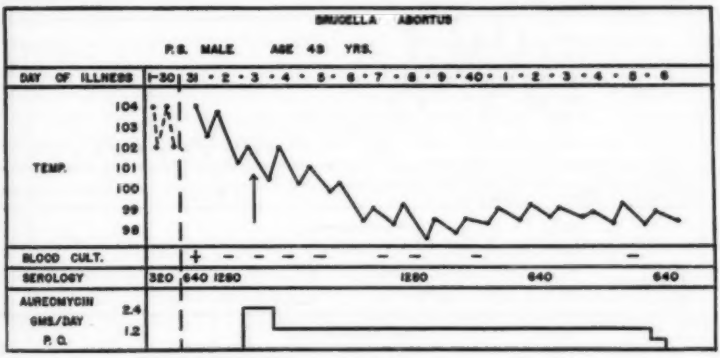

FIG. 2

remained sterile. No marked change was noted in the agglutination titer with brucella during the period of treatment; four agglutination tests taken at intervals were positive in dilutions of 1:640 to 1:1,280.

Therapy with aureomycin was maintained for fourteen days. During this time, the patient received a total of 18 grams of the antibiotic. It was well tolerated and no reactions were observed. He was discharged on his sixteenth hospital day and three months later was still in good health.

Case #3: G. S., a 47 year old male laboratory worker, was first hospitalized on July 21, 1948 with the complaint of weakness and headache for three weeks.

The patient was employed as a laboratory worker and handled the cultures of *Brucella suis* obtained from P. T. (Case #1) for the five preceding months. His fellow worker was J. K. (Case #5). Three weeks before admission, he noted malaise, profuse perspiration, temperature of 102°F., headache, weakness and anorexia. He was given sulfadiazine without relief of his symptoms and his fever

continued between 100°F. and 102°F. Blood serum obtained on the day before admission was found to agglutinate brucella in a dilution of 1:640. He had lost five pounds in weight since the onset of his illness. His past history and family history were noncontributory.

The patient was an asthenic, normally developed and fairly well nourished male who appeared acutely ill. An erythematous flush and small dilated subcutaneous blood vessels were present over his upper chest, neck and face. There were two small erythematous macules medial to his right nipple. Otherwise, his physical examination was essentially normal.

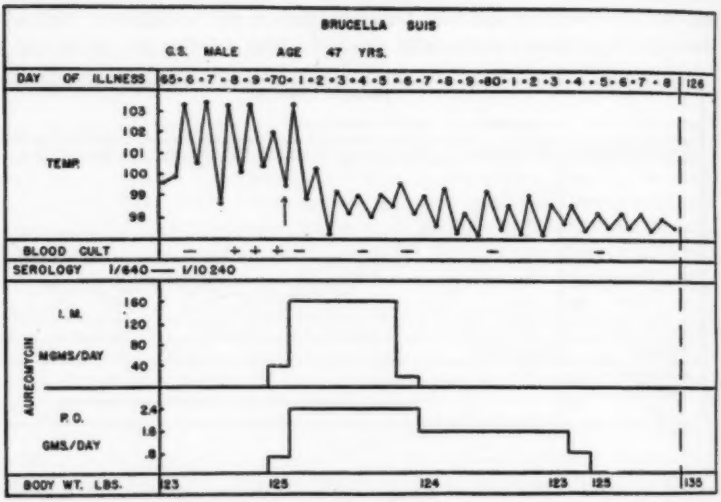

FIG. 3

The patient was discharged after two weeks of observation and bed rest. He had transient pains in his finger joints and erythematous, pruritic wheals while in the hospital. Repeated blood cultures remained sterile but his titers for the agglutination of brucella organisms rose to 1:10,240. No specific therapy was administered on this admission because positive blood cultures were not obtained.

He was readmitted two months later, September 5, 1948, complaining of weakness, migratory erythematous skin lesions, anorexia and muscle pains. Fever which varied between 99.6°F. and 103.5°F. (axillary) and weight loss of ten pounds had been observed. Except for a spleen, palpable three fingerbreadths below the left costal margin, the physical examination was essentially unchanged.

The hemoglobin was 13.6 grams; white cell count 4,500 with 48 per cent neutrophiles, 47 per cent lymphocytes, and 5 per cent monocytes. The corrected sedi-

mentation rate was 38 millimeters (Wintrobe). Urinalyses, chemical examinations of the blood, liver and renal function tests were all normal. Agglutination tests for brucella ranged in titer from 1:640 to 1:10,240. Agglutination tests employing typhoid, paratyphoid A and B and proteus antigens were all negative. A determination of opsonins for brucella revealed a marked increase of phagocytosis, over that of a normal, in the presence of the patient's serum.

In the two days prior to treatment with aureomycin three consecutive blood cultures, subsequently positive for *Brucella suis*, were obtained. The last of these cultures was taken immediately before treatment. Aureomycin was administered orally 200 milligrams every hour for three doses initially and thereafter, 200 milligrams every two hours for six days. It was then changed to 200 milligrams every three hours for eight days. Aureomycin administered by the intramuscular route was used as a supplement in doses of 40 milligrams given every six hours during the first five days. The drug was well tolerated. The patient became afebrile within two days and all symptoms had disappeared by the fourth day of treatment. The spleen decreased progressively in size and was no longer palpable after one week of therapy. Aureomycin was discontinued at the end of two weeks. Six blood cultures taken during the two weeks while on treatment were all sterile. He was discharged from the hospital eighteen days after the initiation, and four days after completion of aureomycin therapy. When seen four months later, he was asymptomatic, afebrile and working. He had gained twelve pounds in weight.

Case #4: W. G., a 37 year old engineer, was hospitalized[5] on October 10, 1948 with the complaint of fever and chills of three weeks' duration.

Two months prior to admission, while visiting on a farm in Florida, the patient drank unpasteurized milk. He remained well until three weeks before entry when he noted generalized weakness, anorexia, malaise, chills and fever which was not influenced by quinine medication. An agglutination test at this time was positive for undulant fever. Past history and family history were non-contributory.

The patient was well developed and well nourished. He appeared acutely ill. The temperature was 102°F., pulse 100, respiration 20. A diffuse erythema was present over the face and neck. The skin was warm and moist. Moderate, tender, generalized adenopathy was present. The liver and spleen were palpable two fingerbreadths below the costal margin. There was slight clubbing of the fingers and toes. A flame shaped subungual hemorrhage was present on the fourth finger of the left hand. The remainder of the physical examination was normal.

Laboratory studies of the blood showed the hemoglobin to be 15 grams with a white cell count of 16,400 and 68 per cent polymorphoneuclearleukocytes and 32 per cent mononuclear cells. The sedimentation rate was 0. Urinalyses, blood chemical studies and liver function tests were all normal. The agglutination titer for brucella ranged from 1:5,120 to 1:10,240. Agglutination tests for typhoid and

[5] Case #4 was admitted to the Church Home and Hospital, Baltimore, Maryland where he was on the service of Dr. Z. Morgan.

paratyphoid A and B were negative. Determination of opsonins for brucella revealed a marked increase of phagocytosis in the presence of the patient's serum. Three consecutive blood cultures taken on the second and third days following admission were positive for *Brucella suis* in two different laboratories.

On the third day of hospitalization, antibiotic therapy was started. Streptomycin 2 grams intramuscularly and sulfadiazine 6 grams orally per day were administered to the patient without manifest change in his condition. After four days, the sulfadiazine and streptomycin were discontinued. The patient was then given aureomycin by mouth, 200 milligrams every hour for three doses, and this was followed by 200 milligrams every two hours for one day. Thereafter, 200 milligrams was administered every four hours for twelve days. The following four days, he received 200 milligrams every two hours. He also was given supplements of aureomycin by the intramuscular route consisting of 40 milligrams every six hours for the first day, and 40 milligrams every twelve hours for ten days. During the entire period he received a total of 18.8 grams of aureomycin. The drug was well tolerated and no nausea or vomiting occurred. Within seventy-two hours after the initiation of therapy, the temperature was normal and the patient became asymptomatic. The spleen and liver decreased progressively in size and were no longer palpable two weeks after the beginning of treatment. The patient was discharged from the hospital seven days after therapy was discontinued. Seven blood cultures taken during the eight weeks concomitant with and following therapy have remained sterile. When seen two months following his discharge from the hospital, the patient had remained well. He had gained ten pounds in weight.

Case #5: J. K., a 53 year old male laboratory worker, was hospitalized on October 22, 1948 complaining of fatigue of two months' duration.

The patient had worked for years as a laboratory helper. He handled the cultures of *Brucella suis* obtained from P. T. (Case #1) four to eight months previously. His fellow worker was G. S. (Case #3). Two months prior to admission to the hospital, he developed malaise, fever, chills and night sweats. This was associated with moderate anorexia and weight loss. One month before entry, he noted the onset of persistent, sharp pains in the left upper quadrant. Ten days before admission, he complained of persistent frontal headache. Because of these symptoms and positive agglutination tests for brucellosis, he was hospitalized. Past history and family history were non-contributory.

The patient was fairly well developed, well nourished and had a marked kyphoscoliosis. He appeared chronically ill. His temperature was 101°F., pulse 90, and blood pressure 120/80. The skin was warm and moist. There was slight epigastric and left upper quadrant tenderness. The liver was firm, smooth and non-tender with the edge palpable four fingerbreadths below the right costal margin. The spleen tip was firm and blunt and palpable four fingerbreadths below the left costal margin. There was no generalized adenopathy and the physical examination was otherwise normal.

His total leukocyte count was 5,500 with a differential of 72 per cent neutro-

philes, 24 per cent lymphocytes, and 4 per cent monocytes. The hemoglobin was 13.8 grams. The corrected sedimentation rate was 22 millimeters (Wintrobe). Urinalyses, chemical examinations of the blood and liver function tests were all normal. Agglutination tests for brucella ranged in titer from 1:160 to 1:10,240. The results of other agglutination tests were: typhoid O negative, typhoid H 1:640, paratyphoid A and B 1:160.

During the twenty-one days prior to aureomycin treatment, five consecutive blood cultures positive for *Brucella suis* were obtained from venous, arterial blood and bone marrow. Four days following the last culture, aureomycin was administered. Unfortunately, the culture drawn the morning before treatment was begun has been lost. The dosage schedule utilized was 250 milligrams every hour for three doses and thereafter 250 milligrams every two hours for eight days. The drug was then continued at a dosage of 250 milligrams every six hours for seven days. Aureomycin given by the intramuscular route in doses of 40 milligrams every eight hours for two days and every twelve hours for two additional days was employed to supplement the oral drug. During this sixteen day period, he received a total of 35.25 grams of aureomycin. The drug was well tolerated but mild nausea and frequent unformed stools occurred on the seventh day of therapy. This was relieved with an aluminum hydroxide preparation and disappeared on continued treatment.

The patient gradually regained his strength and appetite. Night sweats disappeared and within a week he was asymptomatic. His spleen and liver gradually decreased in size. Aureomycin was discontinued after sixteen days of therapy and the patient was discharged one week later. Four blood cultures drawn in the three weeks following the beginning of treatment were sterile. He has remained well for the past two months and has gained five pounds.

SUMMARY OF CLINICAL FINDINGS

Four of these five patients were treated on the eighteenth to the one hundred and third day of their disease. The remaining patient had a three year history characterized by periodic exacerbations and remissions of illness. He was in the thirtieth day of his latest relapse when treated. All patients were males ranging in age from thirty-seven to fifty-three years. All had a history of contact with infected or potentially infected material. Patient #1 worked in a meat packing plant. Patients #3 and #5 as laboratory workers handled the cultures of *Brucella suis* obtained from the blood of Patient #1. Patient #2 was a farmer who drank raw milk and had repeated contact with Bang's Disease in cattle. Patient #4 drank raw milk while vacationing on a farm.

The illness in these five patients was characterized by marked fatigue

which was accompanied or followed by fever, night sweats, muscle pains, anorexia and headache. Four patients complained of shaking

TABLE 2

Summary of Clinical and Laboratory Data

PATIENT	1	2	3	4	5
Initials	P. T.	P. S.	G. S.	W. G.	J. K.
Age	45	48	47	37	53
Sex	M	M	M	M	M
Occupation	Meat packing plant	Farmer	Laboratory Worker	Engineer (vacation on farm—raw milk)	Laboratory worker
Symptoms:					
Fatigue	++++	++++	++++	+++	++++
Sweats	++++	++++	++++	++	++++
Myalgia	++++	+++	+++	++++	+++
Anorexia	++++	+++	++++	+++	++
Headache	++++	++++	++++	++	+
Chills	++++	+	0	++++	++
Arthralgia	+++	0	++++	0	0
Somnolence	0	++++	0	0	0
Signs:					
Fever (°F.)	101–103°	102–104°	99°–103°	100–103°	99–101°
Erythema	++++	0	++++	++++	0
Weight loss	++++	+	+++	++	++
Hepatomegally	+++	0	+	++	++
Splenomegally	0	0	+++	+	+++
Petechial	+++	0	+	++	0
Clubbing	+++	0	0	+	0
Laboratory:					
Blood cultures					
Pre-treatment	13 positive (Br. suis)	1 positive (Br. abortus)	3 positive (Br. suis)	3 positive (Br. suis)	5 positive (Br. suis)
Post treatment	8 negative	7 negative	6 negative	7 negative	4 negative
Agglutination titer	5,120–20,480	320–1,280	640–10,240	5,120–10,240	160–10,240
Previous brucella vaccine	None	None	None	None	None

chills. Only two patients experienced joint pains. Patient #2 was lethargic and disoriented prior to treatment and may well have had a meningo-encephalitis (11, 12). In all patients the fever was of a swinging type with marked diurnal variation. In general, temperatures were lowest in the morning and rose in the afternoon and evening. All

had experienced moderate to severe weight loss. The liver was slightly to markedly enlarged in four cases. In three the spleen was definitely palpable. Erythema of the upper thorax, neck and face, associated with dilated small subcutaneous blood vessels was present in three patients. Petechial and embolic phenomena were most marked in Patient #1. He was observed to have transient, subungual splinter hemorrhages in the fingers, painful erythematous nodules at the tips of fingers and toes, and an organizing hemorrhage near the right macula. This patient had developed definite clubbing of fingers and toes. A soft systolic murmur was intermittently audible at the mitral area. Although splenomegaly was not detected, the diagnosis of an endocarditis due to *Brucella suis* was considered as a distinct possibility (11, 12). Two other patients showed evidence of petechial phenomena. One of these had minimal clubbing of the fingers.

SUMMARY OF LABORATORY DATA

Brucella organisms were isolated from the blood of all five patients prior to the institution of aureomycin therapy. All cultures taken during or following treatment were sterile. Four of the isolated strains were classified as *Brucella suis* and one as *Brucella abortus*. In Patients #1 and #4 cultures of *Brucella suis* were obtained simultaneously but independently in several different laboratories. Prior to therapy with aureomycin, Patient #1 had had thirteen positive blood cultures. Three of these were obtained within ten days and one immediately before administration of aureomycin. Eight blood cultures during the six weeks following treatment were sterile. *Brucella abortus* was cultured from the blood of Patient #2 two days before initiation of therapy. Seven blood cultures taken during the following two weeks were sterile. From Patient #3 *Brucella suis* were grown from three consecutive blood cultures obtained during the seventy-two hour period before treatment was initiated. Six cultures taken during the following two weeks were sterile. Three blood cultures containing *Brucella suis* were obtained from Patient #4 on the fourth and fifth days preceding aureomycin therapy. During the two months following treatment seven cultures were sterile. Cultures of venous blood, arterial blood and bone marrow obtained from Patient #5 all contained Brucella suis. This patient had four cultures containing brucella

organisms drawn during the five days prior to initiation of aureomycin therapy. Four cultures obtained in the three weeks during and following treatment were sterile.

Agglutination titers for brucella in the serum of all patients reached 1:1,280 or higher. Three cases had titers of 1:10,240. One patient had agglutinins for brucella in serum diluted 1:20,480. The remaining patient had a titer of 1:1,280. None of these patients had ever received brucella vaccine or brucellergin skin tests. Tests for opsonins were performed with the serum of three of these patients. A gradual increase in the phagocytosis of brucella organisms exposed to leukocytes in the presence of these sera was noted when compared with normal control sera. Four of the cases showed a mild leukopenia prior to treatment. One patient had moderate leukocytosis. A relative lymphocytosis was observed in all patients at some time during the course of their illness. Erythrocyte sedimentation rates were elevated in four of the five patients. Three of the four cases showed a diminution of the sedimentation rate during or following therapy with aureomycin.

Repeated urinalyses, renal and liver function tests were normal prior to treatment and remained within normal limits during and following the administration of aureomycin. Determinations of blood urea nitrogen, fasting blood sugar, cholesterol, uric acid, creatinine, albumin, globulin, total protein, bilirubin, alkaline phosphatase, thymol turbidity, cephalin flocculation and icteric index in four of these cases remained within the normal range. Although these studies were incomplete in one case, there was no evidence to suggest any abnormality.

SUMMARY OF TREATMENT

An arbitrary oral dosage of 2,400 to 3,000 milligrams of aureomycin (30 to 60 milligrams per kilogram of body weight) per day was initially administered to all patients except the first. A "priming" dose of 200 or 250 milligrams was generally given every hour for three doses. This same dose was then given every two hours for a variable period ranging from one to eight days. The antibiotic was then continued in 200 or 250 milligram doses every three or four hours for a total period of approximately fourteen days. Patient #1 was treated before an oral preparation of aureomycin was available and he received improvised capsules containing 500 milligrams of the crude drug. The latter cap-

sules were given twice a day for four days. In all patients except the second, supplemental aureomycin was administered by the intramuscu-

TABLE 3

Brucellosis

PATIENT			TREATMENT				RESULT**
				Aureomycin			
No.	Initials	Wt.	Previous treatment	Day of disease	Total drug	Dosage schedue	
		lb.			*gm.*		
1	P. T.	135	Streptomycin 3 gm. per day for 11 days. Sulfadiazine 6 gm. per day for 23 days. Polymyxin 420 mgs. I.M. for 10 days	103	6.7	500 mg. q 12 h x 4 days oral 40 mg. q 6 h x 20 days I.M.	Afebrile in 72 hours Asymptomatic in 6 days. No relapse in 8 months.
2	P. S.	185	Penicillin	30*	18.0	200 mg. q 2 h x 1 day oral 200 mg. q 4 h x 13 days oral	Afebrile in 3 days. Asymptomatic in 5 days. No relapse in 3 months.
3	G. S.	123	Sulfadiazine	72	27.0	200 mg. q 1 h x 3 doses oral 200 mg. q 2 h x 6 days oral 200 mg. q 3 h x 8 days oral 40 mg. q 6 h x 5 days I.M.	Afebrile in 48 hours. Asymptomatic in 4 days. No relapse in 4 months.
4	W. G.	171	Streptomycin 2 gm. per day and Sulfadiazine 6 gm. per day for 4 days	18	18.8	200 mg. q 1 h x 3 doses oral 200 mg. q 2 h x 1 day oral 200 mg. q 4 h x 12 days oral 40 mg. q 6 h x 1 day I.M. 40 mg. q 12 h x 10 days I.M.	Afebrile and asymptomatic in 72 hours. No relapse in 2 months.
5	J. K.	110	None	65	35.25	250 mg. q 1 h x 3 doses oral 250 mg. q 2 h x 8 days oral 250 mg. q 4 h x 7 days oral 40 mg. q 12 h x 2 days I.M. 40 mg. q 8 h x 2 days I.M.	Asymptomatic in 7 days. No relapse in 2 months.

* + 3 year history.

** Patients 1, 3, 4 and 5 have been seen since this manuscript was submitted. They were well and examination revealed no evidence of recurrence of their disease. Blood cultures obtained have remained sterile to date (1/27/49).

lar route. Injections of 40 milligrams of aureomycin dissolved in 2 cc. of a 1 per cent procaine hydrochloride solution were administered every

six, eight or twelve hours for four to seventeen days. The total amount of aureomycin employed varied from 6.7 to 35.3 grams and was administered orally and/or intramuscularly during a thirteen to twenty day period. Nausea following the administration of aureomycin by mouth was noted in two cases and was accompanied by vomiting in one. Except for patient #1, who received the crude aureomycin, this nausea subsided on treatment. Aluminum hydroxide preparations were successfully employed to counteract the local gastric irritation. Intramuscular injections of aureomycin dissolved in 1 per cent procaine solution caused considerable pain and induration at the site of injection. Suppuration was not noted. In one patient three to four unformed stools were noted daily on the seventh day of treatment. This patient was receiving a 250 milligram capsule every two hours. These symptoms subsided within two days when an aluminum hydroxide preparation was administered. The dosage of aureomycin had also been reduced to 250 milligrams every four hours.

COMMENT

Four of the above patients had high fever prior to aureomycin treatment. All became and remained afebrile within seventy-two hours after the onset of aureomycin therapy. Symptoms markedly diminished with defervescence. In every case headache, fatigue, night sweats, myalgia, chills, arthralgia and anorexia disappeared during the first week of treatment. When palpable, the liver and spleen progressively decreased in size under therapy. New embolic and petechial phenomena were not observed after aureomycin was administered.

All patients have returned to their former occupations. In each instance a gain in weight followed treatment. This has ranged between five to forty pounds. There have been no relapses. Three patients have been followed for three to eight months. The remaining two patients have remained afebrile and asymptomatic for more than two months. In all patients repeated blood cultures for brucella have remained sterile. It is to be noted that positive cultures for *Brucella suis* were obtained from Patient #1 while he was receiving three grams of streptomycin and six grams of sulfadiazine daily.

Although brucellosis is characterized by an erratic course marked by exacerbations and remissions, it is felt that the results recorded are

sufficiently clear to indicate that aureomycin exerts a beneficial influence in this disease. It is felt that this antibiotic is an effective chemotherapeutic agent for the treatment of undulant fever.

SUMMARY

Studies with multiple strains of brucella including both *Brucella abortus* and *Brucella suis* have indicated that these organisms are sensitive to the antibacterial action of aureomycin *in vitro*. 0.25 to 2.0 micrograms of aureomycin per milliliter of medium completely inhibited growth of eleven strains of brucella during the first seventy-two hours of incubation.

Five patients having blood cultures positive for brucella organisms have been treated with aureomycin. All became afebrile and were markedly improved within forty-eight to seventy-two hours after the initiation of therapy. Positive cultures were not obtained after treatment was begun. When palpable, the liver and spleen receded during therapy, and further evidence of active disease was not observed. Relapses have not been observed during periods of observation after treatment of from two to eight months. Weight gains of five to forty pounds have been noted during this period.

The only toxic reaction associated with oral administration of aureomycin was occasional, transient nausea. This was relieved by aluminum hydroxide preparations. The intramuscular injection of the drug, even when dissolved in 1.0 per cent procaine, produced local pain.

In all but one patient, the initial treatment consisted of 2,400 to 3,000 milligrams orally. Supplemental intramuscular injection of the drug was administered to four patients. The dosage was usually reduced when the patient became afebrile. Aureomycin therapy was continued empirically for approximately two weeks. Supplemental aureomycin injected intramuscularly, may not be necessary for the treatment of brucellosis.

The laboratory and clinical observations in these five cases of brucellosis would suggest that aureomycin is an effective chemotherapeutic agent in this disease.

ADDENDUM

As this paper was being submitted for publication, Spink, *et al.* (J. A. M. A. **138:** 1144, 1948) reported on the treatment with aureo-

mycin of *Brucella melitensis* infections with good immediate therapeutic results.

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EXPERIMENTAL KLEBSIELLA MENINGITIS TREATED WITH INTRATHECAL AND INTRAMUSCULAR STREPTOMYCIN[1]

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The discovery of agents effective in the treatment of the various bacterial meningitides introduced a question which is as yet unsettled, namely; "Is it necessary for the successful treatment of a meningeal infection to effect inhibitory concentrations of the chemotherapeutic agent in the cerebrospinal fluid?" In the absence of data bearing directly on this matter, clinicians have assumed such necessity (1, 2) and there are certain considerations invoked in support of this assumption. The concept of the infected area in meningitis, must include underlying nervous tissues as well as the cerebrospinal fluid and meninges (3–5). In the normal animal such substances as the bromide and iodide ions (6), and the sulfonamides (7) appear in equal concentrations in the brain and cerebrospinal fluid, and presumably in the meninges, when administered systemically. The ability of some chemotherapeutic agents to reach the infected area as judged from these data obtained in normal animals is thus reflected by their concentration in the cerebrospinal fluid. Some agents, such as penicillin and streptomycin, appear in the cerebrospinal fluid (1, 2), and in the brain (8, 9) in negligible concentrations after systemic administration. It was therefore thought that the capacity of these agents to cure meningitis would be poor unless they were injected directly into the cerebrospinal fluid (1, 2). The necessity for intrathecal injection of these antibiotics has recently been reconsidered because 1) such injections are toxic (10, 11) and 2) the use of large doses of antibiotics systemically in the presence of inflamed meninges brings about fairly high cerebrospinal fluid concentrations (9, 12).

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Previous animal studies of the treatment of meningitis have not answered this question because of the low virulence of the infection employed (13, 14). Clinical reports do not permit a conclusion because of the small numbers of cases treated (15, 16), concomitant use of sulfonamides (10, 17) or failure to use comparable controls (18, 19). Therefore, a meningitis in experimental animals was sought which would be suitable for studies of the comparative effectiveness of intramuscular, intrathecal and combined intramuscular and intrathecal administration of a "non-diffusible" antibiotic.

TABLE 1

Effect of Culture Dilution upon Survival Time of 68 Cats Infected Consecutively with K. pneumoniae *Intracisternally*

DILUTION OF CULTURE	NUMBER OF ANIMALS	AVERAGE HOURS OF SURVIVAL
10^{-1}	4	16
10^{-2}	13	19
10^{-3}	6	27
10^{-4}	3	33
10^{-5}	4	35
10^{-6}	35	65
10^{-7}	3	80

MATERIALS AND METHODS

The meningitis produced in cats by Weed et al. (20) using *B. mucosus capsulatus*, was the most virulent of those found in the literature. It was assumed that their organism was a *Klebsiella*, and a trial with a Klebsiella strain produced a satisfactory infection (table 1).

Klebsiella Pneumoniae Infection. The cats were infected with *Klebsiella pneumoniae*, strain BE. Stock cultures were grown in trypticase-soy-phosphate broth. Virulence was maintained by passage through cats, 48 hours before each experiment. For passage 1.0 ml. of a 10^{-2} dilution in modified Ringer's solution (21), of a 6-hour subculture, was given intracisternally, after the withdrawal of a similar amount of cisternal fluid. A culture of cisternal fluid was obtained soon after death, incubated for 6 hours at 37.5° C. and then kept at 6° C. until the day of the experiment.

All untreated cats have died of such infection with positive cultures of the cisternal fluid. Death occurred after the introduction of as few

as 50 organisms. The survival time in the untreated cats was roughly proportional to the culture dilution (table 1). No histological studies were done in this laboratory, although Weed et al. (20) have discussed the pathology of a similar meningitis in their monograph. The proof that this infection is a meningitis rests also on the fact that at the time treatment was started, the cisternal fluid was cloudy and contained innumerable polymorphonuclear leucocytes. In addition, the cultures always became positive and frequently the untreated cats developed the clinical manifestations of meningeal irritation.

For the streptomycin experiment, one ml. of the stock culture was added to nine ml. of TSP broth and incubated for exactly 6 hours. One ml. of a 10^{-6} dilution of this subculture, in modified Ringer's solution, was used for the infection. This inoculum contained an average of 2000 organisms. The first and last cats infected in each experment were saved as untreated controls. A few of the controls received cisternal injections of sterile Ringer's solution, but these cats died more quickly than usual, so the procedure was not made part of the routine.

Streptomycin. A single lot (Pfizer P4718) of amorphous streptomycin sulfate was used for treatment. Chemical assay (22) showed that 77 per cent of this material was streptomycin base. Dosage was calculated in terms of streptomycin base per kilogram of cat. Dilutions were made in sterile modified Ringer's solution. The dose of intracisternal streptomycin was the same for all cats, while the intramuscular dosage varied. The intramuscular drug was given once a day for three days, starting exactly three hours after infection; 50 per cent of the total dose was given in the first injection, and 25 per cent in each of the 2nd and 3rd injections. Intrathecal streptomycin was given in two equal doses at 3 hours and at 24 hours after infection. The intrathecal drug was made up in a dilution of 4 mg. per ml. 0.2 to 1.0 ml. were injected intracisternally in a total dose of 2 mg/kg after the removal of the same volume of cerebrospinal fluid. All the cats were under chloroform anesthesia during the infecting procedure, and, excluding the controls, during the first and second treatments. The cats on intramuscular dosage alone therefore were anesthetized as often as the intrathecal group but did not have additional intracisternal punctures. Sufficient fluid for streptomycin levels could not be obtained.

Cats. The cats constituted an extremely heterogenous group as one cannot obtain cats of the same age, size, and infectional and nutritional backgrounds. Efforts were therefore made to avoid elements of selection. This was accomplished by two maneuvers: 1) The cats were assigned to a given dosage schedule by means of the shuffled card

TABLE 2

Effect of Route of Administration of Streptomycin upon Survival Rate of Cats with K. pneumoniae *Meningitis*

Infection: Intracisternal, 1.0 ml of 10^{-6} dilution of 6-hr. subculture of *K. pneumoniae*, strain BE, containing 2000 organisms.

Streptomycin: Intramuscular, 50% of total dose at 3-hrs., 25% at 27 and 50 hrs. after infection. Intracisternal, total dose constant at 2 mg/kg, 50% at 3 hrs. and 50% at 27 hrs. after infection.

TOTAL DOSE OF INTRAMUSCULAR STREPTOMYCIN	UNTREATED CONTROLS	PROPORTION* OF SURVIVORS		
		Intramuscular	Intracisternal	Intramuscular and Intracisternal
mg/kg				
64		7/7		6/7
32		2/7		5/8
16		3/9		5/7
8		2/11		7/7
4		1/8		5/8
2		2/9		
0	0/19		6/9	

* Numerator represents animals surviving 21 days with negative cultures of blood and cisternal fluid. Denominator represents total animals infected; it excludes animals infected but dying within 21 days with negative cultures. These amount to: intramuscular streptomycin—3 cats at 32 mg/kg, 1 at 4, 1 at 2; intracisternal—1 cat; intramuscular and intracisternal—1 cat at 32 mg/kg, 3 at 16, 2 at 8 and 2 at 4. The difference between numerator and denominator therefore represents animals dying with positive cultures CSF or blood or both.

method, 2) Each single experiment was devised so that it contained each of the 12 dosage schedules shown in the final table. This type of experiment was repeated at weekly intervals, and the results pooled in table 2.

Follow-up. In the first series of experiments the surviving cats were held for at least 21 days after infection, then sacrificed and cultures obtained of the cisternal fluid and heart blood. Similar cultures were obtained from cats dying before 21 days. Eighty per cent of the ani-

mals dying with positive cultures did so in the first week. One cat was found to have a positive blood culture, but negative spinal fluid cultures on the 21st day. Deaths sometimes occurred with negative blood and spinal fluid cultures. Such deaths are noted separately in the table.

RESULTS

The results of the streptomycin treatment of this meningitis are shown in table 2. With combined intramuscular and intracisternal streptomycin treatment, the rates of survival were constant and of the same order of magnitude as with intrathecal drug alone. At each dosage level, except the highest tested, there was a consistent trend in favor of the combined therapy when compared with the group on

TABLE 3

Virulence Titration of K. pneumoniae *Meningitis in Cats Preceding Second Series of Experiments*

DILUTION OF CULTURE	NUMBER OF ANIMALS	SURVIVAL TIME IN HOURS
10^{-2}	1	16
10^{-3}	1	16
10^{-4}	2	26
10^{-5}	2	42
10^{-6}	3	63

intramuscular treatment alone. This consistent difference between the two groups, when considered as a group difference, is statistically significant. With intramuscular drug alone, at dosages from 2 to 32 mg/kg, survivals were erratic, as though streptomycin diffusion occurred in some cats but not in others. When 64 mg/kg were given by the intramuscular route alone, 100 per cent survival was achieved. It seemed important to document further the high survival rate after intramuscular streptomycin alone and therefore a second series of experiments was undertaken.

METHOD

The same procedures and materials were followed as outlined above. The *Klebsiella* was again obtained from Dr. H. J. White. After successive passage through 3 cats, a virulence test was run (table 3). Since virulence did not seem diminished, streptomycin experi-

ments were undertaken. The animals were separated into three groups—untreated controls, treated with intramuscular streptomycin alone, and treated with combined intramuscular and intrathecal streptomycin. The total intramuscular dosage was 128 mg/kg for all cats. The intrathecal dosage was the same as in the first experiment. The animals were followed for two weeks instead of three.

TABLE 4

Effect of High Doses of Intramuscular Streptomycin Alone upon Survival Rate of Cats with Klebsiella pneumoniae *Meningitis*

Infection: Intracisternal; 1.0 ml. of 10^{-6} dilution of 6-hr. subculture of *K. pneumoniae* containing 2000 organisms.

Streptomycin: Intramuscular; Total dose 128 mg/kg, divided into 3 doses, 50% at 3 hrs., 25% at 27 and 50 hrs. after infection. Intracisternal; Total dose 2 mg/kg, 50% at 3 hrs. and again at 27 hrs. after infection.

	UNTREATED CONTROLS	INTRAMUSCULAR STREPTOMYCIN	INTRACISTERNAL & INTRAMUSCULAR STREPTOMYCIN
Total Infected	11	23	20
Survived 14 Days with Negative Cultures		13	10
Died in less than 14 Days with Negative Cultures		9	10
Died with Positive Cultures	11	1	0

RESULTS

The effect of high intramuscular dosage is shown in table 4. A number of deaths occurred before the 14th day, because of an epidemic of pneumonitis. The entire experiment is shown, although conclusions should only be drawn from the survivors. Only one cat died with a positive culture, and this was of the blood only. It is clear that intramuscular drug alone, in large doses, can routinely bring about survival from the infection.

DISCUSSION

It has not been possible in this study to examine directly the relationship between survival of the infected cats and the actual concentration of the streptomycin in the cerebrospinal fluid. Nevertheless, the data permit the inference that it is the streptomycin reaching

the cerebrospinal fluid that represents the ability of the drug to overcome the infection. In other words, this infection seems to be in equilibrium with the drug in the cerebrospinal fluid. This principle has been examined under rigid and therefore artificial conditions and its applicability to clinical meningitis can be determined only by direct examination in patients. Certain points must be made however, so that conclusions from these data will not be over-extended. One can only conclude that in the treatment of meningitis in patients, chemotherapeutic agents should continue to be used in such a manner as to insure their appearance in the cerebrospinal fluid in antibacterial concentrations. It should not be assumed that intrathecal injection of penicillin or streptomycin into the lumbar region is the best way of distributing the drug to the entire infected area. In general, the concentration of intrathecally administered drugs, such as bromides, is greatest at the site of injection, and in other areas diminishes in proportion to its distance from the point of injection (6). With penicillin, the concentration in ventricular fluid after lumbar injection is variable and sometimes negligible (23). On the other hand, when substances such as bromide or iodide anions (6) or salicylates (24) appear in the cerebrospinal fluid after systemic administration equal concentrations are found in all parts of the cerebrospinal fluid, even below a complete block. In the treatment of meningitis with drugs that are not readily transferred from the plasma to the cerebrospinal fluid, intrathecal injection in the lumbar area is probably an inefficient way of getting the drug into the infected area. It would seem more desirable to accomplish the transfer of drug from blood to cerebrospinal fluid. Efforts in this direction have been made by the use of caronamide and large doses of penicillin (25), and by the use of 12 million units daily of intramuscular penicillin alone (15). These methods would appear to accomplish transfer of penicillin to the cerebrospinal fluid in antibacterial concentrations. Whether such methods are as effective treatment of clinical meningitis as intrathecal injections must be subjected to cautious study in patients.

The toxicity of intrathecally administered antibiotics is another objection against the direct injection of these agents into the cerebrospinal fluid. However, one suspects that for any given concentration of the drug, the general toxicity would be the same whether the agent

reached the cerebrospinal fluid by direct injection or by transfer from the blood. The local toxicity of the antibiotic might be greater after intrathecal injection because the unreliable distribution from the lumbar route requires the administration of fairly large amounts of drug in order to achieve antibacterial concentrations throughout the cerebrospinal fluid. Thus, 20,000 units of penicillin given intrathecally in a volume of 10 ml. may give a local concentration in the lumbar spinal fluid of > 700 units/ml (23). Hence the problem again returns to finding a better method of distributing antibiotics throughout the infected area.

SUMMARY AND CONCLUSIONS

1) A highly virulent uniformly fatal meningitis has been induced in cats by intracisternal injection of *Klebsiella pneumoniae*.

2) Treatment by means of intrathecal, intramuscular, or combined administration of streptomycin, suggests that survival of the cats is governed by the amount of drug that reaches the cerebrospinal fluid.

3) Survival of the infected cats occurs routinely when large doses of streptomycin are given solely by the intramuscular route.

4) The possible clinical implications of these data are discussed, with emphasis on the deficiences of the lumbar intrathecal route as a method of distributing the antibiotic to the infected area.

The author wishes to thank Dr. H. J. White of the American Cyanamid Company for the culture of *K. pneumoniae*, Dr. Margaret Merrell, School of Hygiene and Public Health, The Johns Hopkins University, for advice on statistical matters; and Dr. R. A. Patelski of Chas. Pfizer and Company for the streptomycin sulfate.

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THE PREVENTION AND TREATMENT OF MOTION SICKNESS*†

I. SEASICKNESS

LESLIE N. GAY AND PAUL E. CARLINER**

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1. INTRODUCTION

Scientists have been puzzled by their inability to find a remedy for the disease known as motion sickness. No record to date is published of any drug which has satisfactorily prevented, allayed, or cured this unfortunate malady. Many investigators have studied motion sickness, especially during World War II, and many drugs have been used in an attempt to control its symptoms, but no drug that can be used liberally and repeatedly has been found. Drugs which were apparently successful often produced side effects as seriously handicapping as motion sickness itself. Careful study has proved hyoscine the most effective drug so far employed. Hollings, McArdle and Trotter (1) in 1944, on behalf of the Medical Research Council of Great Britain, studied the effect of a number of drugs on short trips to sea in minesweepers and trawlers. These trips were of two to six hours' duration. The side effects from hyoscine were such that they did not recommend repeated doses. Tyler (2) in 1946, under contract with the Committee on Medical Research of the United States, studied the influence of a placebo, body position, and medication on motion sickness. He showed that the psychogenic factors play little part in susceptible individuals. He placed a large number of men in small boats (amphibious operations) gave to half of them a placebo and to half no medication. Thirty-five per cent of each group became

* This investigation was made possible by the Chief of Staff and the Surgeon General of the United States Army.

Appreciation is expressed to the Transport Command, especially to Major C. W. Hodges, Lt. J. L. Soelling and to the nurses, of the U.S.A.T. General Ballou.

† The authors wish to express their appreciation to G. D. Searle & Co. of Chicago, who prepared the drug Dramamine and the placebo for the investigation.

** From the Allergy Clinic of the Medical Department of the Johns Hopkins University and Hospital.

ill in shore to shore operations. In the untreated control group thirteen per cent had severe symptoms and in the placebo treated group fifteen per cent had severe symptoms. The position which men occupied in small boats played a part in the number of ill men, as well as in the severity of symptoms. In a crouching position thirty per cent became seasick; in the standing position eleven per cent became ill. Ten per cent of the crouching men were very sick compared with two per cent of the standing men. Medication was more effective than a placebo. Barbiturates were very unsatisfactory, and hyoscine afforded an average of sixty per cent protection when placebo rates were as high as fifty-two per cent. Noble, Sellers, and Best (3), in an investigation sponsored by the National Research Council of Canada in 1947, studied swing sickness in dogs and in man and reported that "while a correlation between swing sickness and sea or air sickness could be shown to exist it did not appear to be of high order." The belladonna alkaloids which they used to control symptoms produced three side effects which were objectionable: hallucinations, excited states and mental cloudiness. The mental cloudiness occurred most prominently with hyoscine, especially common with 0.8–1.2 mg. It is of interest to note their comment that atropine, hyoscine and hyoscyamine are totally inactive in preventing motion sickness in dogs. The authors state that attempts to make sea trials using large numbers of subjects "were ruined by fair weather." Lilienthal (4) reported the effect of hyoscine on airsickness. He found that 0.6 mg. administered orally 30–60 minutes before flight was a preventive of airsickness with insignificant side effects. He did not report concerning the effect of hyoscine on combat troops when administration of the drug becomes necessary every few hours, as is the case when a landing operation must be carried on many miles from the base of origin.

A compound thought to be more uniformly effective in the prophylaxis and treatment of motion sickness than any drug so far employed and without unpleasant side effects is the subject of this report. In 1947 a new drug, Dramamine, was sent by the manufacturers* to the Allergy Clinic of the Johns Hopkins University and Hospital for experimental investigation of its possible value in the control of hay

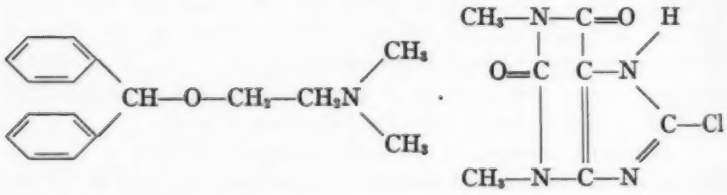
* G. D. Searle & Co., Chicago, Illinois.

fever and urticaria. Among other patients, the drug was administered to a pregnant woman with urticaria who incidentally had suffered all her life from car sickness. It was possible to control the car sickness of this patient at will. A placebo failed repeatedly, but Dramamine gave complete relief if she took 50 mg. a few minutes before she boarded a streetcar.

Subsequent to this isolated clinical observation, other victims of car sickness and airsickness sought among patients and friends were, without exception, completely freed of discomfort, provided the drug was taken just before exposure to the motion of the respective means of transportation.

In the summer of 1948 an opportunity to use the drug extensively on the U. S. S. America presented itself. The surgeon, Dr. John E. Sheedy, and nursing staff on this vessel cooperated in every detail, and with their assistance sufficient data were collected during four months to warrant a more extensive and intensive study of Dramamine in motion sickness. A brief report on the study carried out on the U. S. S. America was submitted to the Chief of Staff and to the Surgeon General of the U. S. Army. The control of seasickness is so important to military operations that complete cooperation for the present study was immediately obtained, and "Operation Seasickness" on which this report is based was planned to begin on November 27, 1948.

2. PHARMACOLOGY AND TOXICOLOGY OF DRAMAMINE



The pharmacology and toxicology of Dramamine have been examined in the laboratory of the manufacturer, and the data which follow are based on these studies. Dramamine is β-dimethylamino-ethyl benzohydryl ether 8-chlorotheophyllinate, and contains 54.3 per cent of the ether. It is relatively insoluble in water.

Antihistaminic potency, measured by the method of Loew, Kaiser and Moore (5), was found to be $1\frac{1}{2}$ times as great as β-dimethylaminoethyl benzohydryl ether on the basis of the ether content. Spasmolytic activity, determined by the Magnus technique (6), was found to be less than that of the ether. This is probably due to the insolubility of Dramamine.

Blood pressure and respiration studies were done on cats under pentobarbital anesthesia. In doses of 3–12 mg./Kg., administered intravenously, Dramamine caused a transient fall in blood pressure ranging from 29 to 56 per cent with a return to normal in from 1 to 3 minutes. Respiration was slightly accelerated.

Acute, subacute and chronic toxicity in various animal species were as follows:

a) Acute toxicity: in the mouse the LD_{50} by the intraperitoneal route was 149 mg./Kg.; by mouth 203 mg./Kg. In the rat the LD_{50} by the oral route was 1,320 mg./Kg.

b) Subacute toxicity: 50 mg. to 100 mg./Kg., given daily over a period of 2 to 8 days, caused the death of six cats.

c) Chronic toxicity: large doses were adminisered orally to eight rats, divided equally between the sexes. The test ran for 63 days with an average daily intake of 22 mg./Kg. There was no weight loss during the experiment. Each animal was weighed every week, and weekly complete blood counts remained normal. After 63 days, half the animals were sacrificed for postmortem examination by decapitation. Administration of the drug to the remaining two males and two females was continued for a total of 119 days, when they, too, were sacrificed. Two normal litters were born to each female before the experiment was terminated. As controls, an equal number of normal rats maintained under identical conditions but untreated with Dramamine were sacrificed at the same time intervals. These animals in the acute, subacute and chronic toxicity experiments showed no gross or microscopic deviation from normal at autopsy.

The data indicated that the oral administration of Dramamine given in doses of 50 to 100 mg. every four hours for a period of 6 to 10 days provided an ample margin of safety. However, they provided no information as to the possible frequency of the minor disagreeable side effects produced by other antihistaminic compounds .

3. PLAN OF EXPERIMENTAL STUDY

To carry out the study of motion sickness at sea, the following plans were made:

a) An Army Transport, the U. S. A. T. General Ballou, carrying 1366 replacement troops to Germany was chosen. This 13,000 ton ship had been constructed for the U. S. Navy for use as a freight transport ship on the Pacific. It was converted into a troop transport with most compartments below the water level. Because of its construction—narrow and high out of the water—a transatlantic passage would be rough, even in the mildest of seas. A diagram of the interior arrangements is shown in Figure I.

b) The compartment construction of this ship made it possible to assign 500 men in four adjacent sub-level compartments, thus all lived

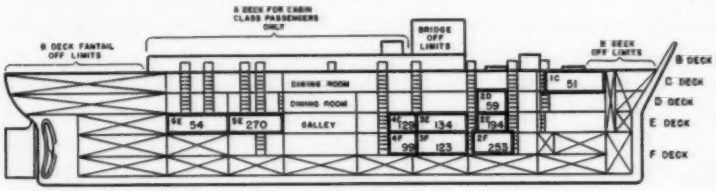


FIG 1

under similar conditions and were subjected to the same motion of the sea.

The U. S. A. T. General Ballou is a small ship with limited deck space for promenades and with a very small troop lounge. Weather conditions prevented the men from enjoying the upper deck. Consequently the soldiers who took Dramamine and the placebo were compelled to live in the same confined conditions and were subjected to the same movements of the ship. Compartments 3-E, 3-F, 4-E, and 4-F were set aside for the study of 485 men, distributed in these compartments. These men were divided into two groups, A and B.

Group A (prophylactic trial) was divided into two sub-groups: Sub-group I, 134 men, occupied compartment 3-E; sub-group II, 123 men, occupied compartment 3-F.

These two sub-groups were given the following treatment:

Sub-group I: When the transport left the harbor of New York, each

of the 134 men in compartment 3-E was given orally a capsule containing 100 mg. of Dramamine. The same dose was repeated six hours later at bedtime. For two days after the ship put to sea, a capsule of 100 mg. was given to each man before each meal and another on retiring, a total of 400 mg. daily.

Sub-group II: When the transport left the harbor of New York, each of the 123 soldiers in compartment 3-F was given a placebo capsule containing lactose identical in appearance to the capsule containing the drug. For two days after the ship put to sea, the same schedule was maintained with the placebo as with Dramamine.

Group B (therapeutic trial) was divided into two sub-groups: Sub-group III, 129 men, occupied compartment 4-E; sub-group IV, 99 men, occupied compartment 4-F.

Prophylactic treatment was not given to these two sub-groups. All men were kept under close observation because it was desirable to determine the effectiveness of the drug on individuals after seasickness had developed. It was impossible to anticipate the number of sick individuals. Nevertheless, it was planned to give the drug to all 4-E men who developed motion sickness, and a lactose placebo to all 4-F men who developed motion sickness.

c) A protocol was maintained on every individual who developed seasickness, and daily conferences were held with every seasick person after the vessel left New York and throughout the voyage to Bremerhaven, Germany.

d) Since the voyage required a minimum of ten days, satisfactorily rough weather was anticipated, especially in midwinter. With a variety of rough and smooth weather, varying severity of seasickness was to be expected, especially on a vessel noted for its roll and pitch in a calm sea. Accurate weather conditions were recorded by the ship's officer each day and a comparison of weather with the number of seasick soldiers and with the severity of symptoms was thus facilitated.

e) Each compartment was placed in charge of a non-commissioned officer who was responsible to the ship's Medical Officer. The non-commissioned officer who had no knowledge of the contents of either capsule personally administered the drug or the placebo to his men and observed that each capsule was swallowed. He was also responsible for the attendance of every ill soldier referred to the sick bay. Under

military discipline there is no difficulty in obtaining complete cooperation. To insure the cooperation of all soldiers in these four compartments, a sheet of printed instructions was given to each member of the experiment but the substitution of a placebo containing lactose instead of the drug was not mentioned. The reason for the administration of the drug was explained in detail; therefore, each soldier knew that the object of the experiment was to prevent or cure seasickness, a malady of which he had some knowledge, even though personal experience with motion sickness might be lacking.

f) In addition to the four compartments set aside for intensive study, there were 881 soldiers distributed in six other compartments. Opportunity to treat any seasick soldier in this group had been anticipated and since the rumor of the experiment spread throughout the transport, a great number of men reported or were carried to the sick bay for treatment. These compartments were: 1-C, 51 soldiers; 2-D, 59 soldiers; 2-E, 194 soldiers; 2F, 253 soldiers; 5-E, 270 soldiers; 6-E, 54 soldiers.

4. THE EXPERIMENTAL STUDY

The experiment was begun as planned, just as the U. S. A. T. General Ballou left New York at 3:30 P. M. on Saturday, November 27, 1948.

Weather conditions were moderately rough for the first five days with a roll of 4 to 15 degrees, and violently rough for the remaining five days with a heavy roll of the vessel from 22 degrees to as high as 35 degrees.

Interviews with sick troops were held in the morning between 9:00 A. M. and 11:30 A. M., in the afternoon between 3:00 P. M. and 5:00 P. M. and in the evening after 7:00 P. M. Leading questions were avoided. These interviews were recorded on individual protocols by the investigators themselves. During the last 48 hours aboard ship 311 soldiers who had been seasick reported for a final interview.

5. RESULTS OF THE EXPERIMENTAL STUDY

Each compartment in the experimental groups A and B is reported in detail. *Group A—Sub-group I—Compartment 3-E:* (Table I-a and b) This group of 134 men continued the prophylactic dose of Dramamine (400 mg. daily) for a minimum of 48 hours. Of the 134

men who were given Dramamine 100 mg. on embarkation and four times daily not one man developed nausea or vomiting while taking

WEATHER REPORTS

*On Board U.S.A.T. General Ballou November 28 to December 6 Inclusive, 1948**

DATE	TIME	WEATHER	SEA
1948			
11/28	0000	clear	Moderate sea and swell Vessel pitching moderately
	1200	cloudy	Moderate to rough sea and swell Vessel rolling up to 12°
11/29	0000	cloudy	Moderate to rough sea Average swell—Vessel rolling moderately to heavy 15°
	1200	rain	Moderate sea and swell Vessel rolling to 8°
11/30	0000	rain	Moderate swell—Vessel rolling to 5°
	1200	rain	Moderate to rough—Confused swell Vessel rolling to 9°
12/1	0000	cloudy	Moderate—Vessel rolling gently Maximum roll—4°
	1200	cloudy	Rough sea—Heavy swell—Vessel pitching—Rolling heavily up to 28°
12/2	0000	squalls	Rough sea—Heavy swell—Vessel rolling heavily to 22°
	1200	squalls	Very rough sea and heavy swell Vessel rolling up to 35°
12/3	0000	cloudy	Swell heavy—Vessel rolling moderately to heavy up to 19°
	1200	overcast	Moderate to heavy swell—Vessel rolling heavy up to 24°
12/4	0000	squalls	Very rough heavy swell—Vessel rolling moderately to heavy up to 12 to 15°
	1200	rain	Rough sea and heavy swell Vessel rolling 25 to 28°
12/5	0000	rain	Very rough sea—heavy swell
12/6	0000	cloudy	Moderate sea—low swell

* Temperature recordings, barometric pressure, and wind direction omitted as unimportant.

the drug and only two men complained of some dizziness. The 134 men maintained excellent morale, even complained that they were unable to satisfy their appetites. Treatment was then discontinued

entirely on this group for 18 hours, at the end of which time all men who had developed seasickness were advised to report to the sick bay. Forty-one men (30.5 per cent) reported that seasickness had developed 10 to 18 hours after the drug had been omitted. For these men

TABLE I-a

Prophylactic Trial

	COMPARTMENT	
	3-E	3-F
Number of men	134	123
Treatment	Dramamine*	X-23 (placebo)
Hours of treatment	48	48
	No. *%*	*No.* *%*
Cases of seasickness	2 *1.4* (dizziness only)	35 *29*** (nausea, vomiting, dizziness)

* Drug dose = 100 mg. before each meal and before retiring.

** The difference in percentage relief is significant at odds of approximately 1:60.

TABLE I-b

Therapeutic Trial

COMPARTMENT 3-E (134 men)			COMPARTMENT 3-F (123 men)		
	No.	%		No.	%
Number of men who developed seasickness after discontinuing Dramamine	41	*31*	Number of men who developed seasickness while on X-23	35	*29*
Dramamine prescribed					
Complete relief after ½ hour	40	*98*	Complete relief after ½ hour	34	97
Partial relief	1	*2*	Partial relief	1	3

Dramamine was again prescribed: 50 to 100 mg. before each meal and on retiring. After 24 hours, one of the 41 men still complained of slight dizziness, but 40 had regained their normal state of health within ½ to 1 hour after the first dose. Dramamine was administered to these 41 men by the non-commissioned officers every four hours for two days. It was then discontinued. Within twenty-four hours all 41

again reported to the sick bay either because of a second recurrence of severe seasickness, that is nausea and vomiting, or because of inability to retain food or water for at least twelve hours. Dramamine was again administered, and within one hour all but one man were completely relieved. This man continued to complain of some dizziness, but subsequently was able to retain food and water. These 41 men then continued the treatment without recurrence of seasickness before arrival at Bremerhaven.

Group A—Sub-group II—Compartment 3-F: (Table I-a and b) This group of 123 men continued the placebo according to the schedule for 48 hours. As contrasted with the almost complete absence of seasickness in the group treated with Dramamine, 35 men (28.4 per cent) reported that seasickness had developed within 12 hours after departure from New York harbor. These men, who had severe symptoms, continued the placebo for the two day period, after which time Dramamine was prescribed. They were given 100 mg. of Dramamine which was continued at a dosage level of 400 mg. daily and, with the exception of one man who still complained of dizziness, this group obtained complete relief within one hour after the first dose. Two days later, three men omitted the drug, symptoms returned after six hours, the drug was again prescribed, and each man was relieved within one hour after his first dose. This group of 35 men continued treatment until arrival at Bremerhaven.

Group B—Sub-group III—Compartment 4-E: (Table II) This group of 129 men remained under observation, but treatment was withheld until severe symptoms had developed. Within 12 hours after departure from New York, 15 (11.6 per cent) reported to the sick bay. Dramamine was prescribed, 100 mg. every five hours and on retiring. Fourteen were immediately relieved of their symptoms and one obtained partial relief. After two days, eight men omitted the treatment; but because of a return of severe symptoms, treatment was again initiated with complete relief of seven and partial relief of one. These 15 men continued treatment and remained free of symptoms until arrival at Bremerhaven.

Group B—Sub-group IV—Compartment 4-F: (Table II) This group of 99 men was the control group for compartment 4-E. Within 12 hours after departure from New York, 33 (33.3 per cent) reported to the

sick bay. These men were given a placebo, one capsule every five hours and upon retiring. Two days later, they again reported to the sick bay and the following facts were recorded: nineteen men whose complaints had been nausea and dizziness had recovered within 12 hours. The lactose treatment of the 19 men was discontinued, and they had no return of symptoms during the remaining days of the voyage. Fourteen men became progressively worse on the placebo and now complained of excessive nausea, extreme dizziness and prolonged vomiting. The 14 men whose symptoms had become pro-

TABLE II

Therapeutic Trial

Compartment Number of men Treatment	4-E 129 Dramamine*		4-F 99 X-23 (placebo)	
	No.	%	No.	%
Cases of seasickness within 12 hours after departure	15	*12*	33	*33*
Complete relief within ½ hour	14	*93***	19	*58***
No relief	1	*7*	14	*42*
			Dramamine prescribed to above 14 men and complete relief obtained in ½ hour.	

* Drug dose = 100 mg. before each meal and before retiring.

** The difference in percentage relief is significant at odds of approximately 1:60.

gressively worse on the placebo were then given capsules of Dramamine according to the schedule (every five hours and upon retiring). Complete relief followed in all 14 within one-half hour after the first dose of 100 mg. After two days three men discontinued the drug, symptoms returned, and again the drug was prescribed. These men again completely recovered one-half hour after the first dose. The 14 men then continued the treatment and remained free of symptoms until the completion of the voyage to Bremerhaven.

Among the men in compartments 1-C, 2-D, 2-E, 2-F, 5-E and 6-E, none of whom received prophylactic treatment, there were many

instances of seasickness, and these men were treated with the drug and with a placebo (Table III-a). They were followed with the same care as were the men in the experimental groups A and B. Valuable

TABLE III-a

Therapeutic Trial

Combined compartments	1-C, 2-D, 2-E, 2-F, 5-E and 6-E	
Number of men	881	
	No.	%
Cases of seasickness	195	*22*
Dramamine		
Complete relief	187	*96*
No relief	8	*4*
Treatment discontinued after 2 days	187	
Relapses	44	*24*

TABLE III-b

Treatment of Relapses

Number of men	44	
	No.	%
Group a—Dramamine	18	
Complete relief	15*	*83***
No relief	3	*17*
Group b—X-23 (placebo)	26	
Complete relief	2	8**
No relief	24	92
Group b—Dramamine—subsequent treatment	24	
Complete relief	16*	
Unreported†	8	

* Complete relief was obtained in every instance within one hour after the first capsules of Dramamine (50 to 100 mg.)

** The difference in percentage relief is significant at odds of approximately $1:10^6$.

† Eight men failed to report at time of final conference.

information, which supplemented that of the experimental groups, was obtained.

The number of occupants in these six compartments totaled 881. During the voyage 195 (22.1 per cent) of these men reported severe

symptoms of seasickness. Each one immediately began treatment with Dramamine, 100 mg. every five hours and on retiring. Of this group of 195 men, 187 were completely relieved within one hour after the first capsule, but 8 derived no benefit from the 400 mg. admin-

TABLE IV

Summary of Therapeutic Use of Dramamine

Total number of men on board—U.S.A.T. General Ballou	1366	
Total number of cases of seasickness	319	
Total number of cases of seasickness treated with Dramamine and recorded	300	
Complete relief obtained	288	96.0%
Partial relief or failure	12	4.0%
Total number of relapses induced by omission of Dramamine	89	
After Dramamine complete relief obtained	84	94.4%
After Dramamine partial relief or failure	5	5.6%
Total number of cases treated with Dramamine including relapses	389	
Complete relief obtained	372	95.6%
Partial relief or failure	17	4.4%

TABLE V

Number and Percentage of Failures of Response to Dramamine Compared with Similar Failure with Placebo

	DRAMAMINE			X-23 (PLACEBO)		
	No. treated	No. failures	% failures	No. treated	No. failures	% failures
Prophylactic use	134	2	1.4*	123	35	28.4*
Therapeutic use	319	8	2.5*	59	38	64.4*

* The difference in percentage protection or relief between the Dramamine and placebo group is significant at odds of approximately $1:10^6$.

istered daily. After two days of treatment the drug was discontinued in these 187 men and 44 of this group then developed nausea and vomiting within twelve hours.

In order that additional confirmatory information concerning the value of the drug could be gathered, the above group of 44 was divided

and treated as follows: 18 men were given Dramamine, 400 mg. daily (Table III-b). Within one hour after the first dose, symptoms were completely relieved in 15, but there was no improvement in 3. Twenty-six were given a placebo, a capsule every five hours and on retiring; after 24 hours these men were interviewed and 2 had regained their normal condition but 24 were unimproved or worse. These men complained that the capsules (which they did not know contained lactose) had made them much worse, therefore, these 24 men were then given Dramamine and were advised to report on their condition the following day. Sixteen appeared at the sick bay. Of this number, only one man failed to be relieved within one hour after the first capsule of 100 mg. It was impossible to obtain information from 8 men of the group of 24 because of the termination of the voyage.

6. DISCUSSION

Seasickness is an acute illness which may clear spontaneously within two or three days after onset when the apparatus of equilibrium accustoms itself to the motion of a ship at sea. The serious manifestation is the chronic state, characterized by nausea, dizziness and vomiting of such violence that dehydration followed by acidosis occurs. Travelers on commercial liners have no conception of the seriousness of the condition, as the "afflicted" remain in their cabins, attended by stewards, or they lie prostrate on deckchairs. With nursing and encouragement to take fluids serious complications are usually avoided. No such service is available on a troop ship, and only those who have accompanied troops at sea can realize the administrative problem.

A brief description of the voyage to Bremerhaven will enlighten those who are not aware of the complications. Within twelve hours after the U. S. A. T. General Ballou left New York harbor, the corridors of compartments were congested by sick men, so ill that they were unable to reach the latrines. The men who reached these areas were unable to return to their compartments and remained stretched out in semi-conscious condition on the floors until more seaworthy individuals managed to drag them to the sick bay or back to their hammocks. The latrines became temporarily indescribably repulsive. According to the ship's surgeon, such an overwhelming sickness would have

filled the forty available beds in the sick bay and then, because of inadequate help, dehydration would have followed. On the previous trip of the U. S. A. T. General Ballou from Bremerhaven, more than 100 intravenous injections of saline solution were required to relieve a number of dehydrated persons. This necessitated continuous work, night and day, throughout the trip and consequently it was necessary to neglect other important duties.

In order to prevent a repetition of similar disorder, all seasick soldiers were given Dramamine as soon as they reached the sick bay and treatment was continued according to the schedule previously outlined. During the ten days at sea, the administration of Dramamine successfully controlled all severe symptoms in every seasick soldier with the exception of 8 men. No soldier required hospital admission or intravenous treatment.

When the control subjects developed seasickness, many were brought to the sick bay in a semi-conscious state. A number had lain in their hammocks for three days without food or drink and consequently could not walk or even stand when they were brought to the surgeon's office. Many lay stretched out on the floor, too ill to retain even a capsule of the drug. To overcome this difficult situation, the drug was administered rectally. The capsule was punctured at each end, inserted into the rectum, and 30 cc. of salt solution was injected into the rectum. With rectal, as well as oral administration, relief was prompt. Within one-half hour, the sick soldier had improved to such an extent that he was aware of his surroundings; soon he asked for fluids and within an hour he was able to retain both fluids and solid food. These dramatic examples occurred repeatedly during the 10 days of this experimental study, and gave information as to what might be accomplished by rectal administration of the drug, when the patient was unable to retain oral medication.

The action of Dramamine on the prevention and control of motion sickness is as yet not definitely established. Studies are in progress to attempt to explain the mechanism.

Throughout the duration of this experiment, careful watch was maintained for unpleasant symptoms from the drug but in no instance, even though thousands of capsules were administered to more than 300 men, was there a complaint or evidence of discomfort which neces-

sitated discontinuance of treatment. This observation differs from the reaction to other antihistaminic drugs, which, when used for the control of allergic manifestations, cause unpleasant symptoms in 25 to 60 per cent of patients. The usual amount of Dramamine required to prevent symptoms was 400 mg., in 24 hours; in a few instances, as much as 800 mg. of the drug was necessary.

It was of interest to note how many of the men who developed seasickness on their voyage to Bremerhaven had previously been at sea. Of 608 men questioned, only 78 had been to sea on one or more former occasions. Forty of these had experienced seasickness on their earlier trips.

7. CONCLUSIONS

The accumulated data indicate that Dramamine is a powerful, nontoxic, prophylactic and therapeutic drug, which can be used to control the symptoms of seasickness. The drug may be taken orally or it may be administered rectally, and no untoward side effects have been noted, using the standard dose of 400 mg. In a group of more than 300 men, who developed moderate to violent symptoms of seasickness while en route to Bremerhaven, complete relief was obtained in all but 11 cases.

SUMMARY

1. A study of seasickness was planned and executed on the U. S. A. T. General Ballou.

2. This transport carried 1366 soldiers to Bremerhaven, Germany. The voyage began on November 27, 1948 and, after a rough passage, terminated on December 7, 1948. Complete cooperation was given by the Surgeon General's office and by the Transport Command.

3. Four compartments on the transport were set aside for the controlled study of the 485 men assigned to these compartments and subjected to the same motion of the sea.

4. Treatment was planned so that half of the men were given Dramamine or a placebo at the time of departure from New York harbor; the other half were given Dramamine or a placebo 2 to 12 hours after the onset of symptoms of seasickness. Adequate control groups were given a placebo. The dose of Dramamine was 100 mg. every five hours and before retiring.

5. Dramamine prevented seasickness in all but 2 men of 134 who occupied compartment 3-E; the placebo failed to relieve the symptoms in all controls who developed true seasickness in compartment 3-F. However, this control group (34 men) obtained complete relief of symptoms within one hour after the first dose of Dramamine was administered.

The drug gave complete relief to 14 men in compartment 4-E who developed symptoms three or more hours after the transport left New York. A placebo failed to relieve 14 men in compartment 4-F but these men obtained complete relief one-half hour after Dramamine

TABLE VI

Return Trip of the U. S. A. T. General Ballou from Bremerhaven

Total number of seasick passengers	109	
	No.	%
Dramamine prescribed	73	*100*
Complete relief	65	*89*
24 hours	56	
48 hours	9	
Partial relief	5	*7*
No relief	3	*4*
Placebos prescribed	36	
Complete relief (24 hrs.)	16	*44*
No relief	20	*56*
Dramamine prescribed	20	
Complete relief	14	*70*
Partial relief	6	*30*

was substituted for the placebo. Nineteen men who developed symptoms three or more hours after the transport left New York recovered while on a placebo. These men required no medication during the last seven days of the voyage to Bremerhaven.

6. Among 881 men who occupied other compartments on the transport, 195 cases of severe seasickness developed. Of these, 187 derived complete relief one-half hour after the administration of Dramamine.

7. Relapses were induced by the substitution of a placebo, but these symptoms were relieved within one-half hour after the administration of Dramamine. (Table IV)

8. During a period of 10 days, Dramamine was given to 389 cases of seasickness. Of this number, 372 were completely relieved of symp-

toms within one hour after the first dose of 100 mg. Seventeen cases derived only partial or no relief. (Table V)

9. A dose of 100 mg. prescribed every five hours and before retiring was adequate to control the most distressing symptoms. When the patient was unable to retain a capsule administered orally, he did retain and absorb the drug given rectally. The benefit derived by this route of administration was as rapid and as complete as that derived by the oral route.

10. No reaction to Dramamine was encountered by any soldier to whom it was administered during the period of ten days.

SUPPLEMENTARY NOTE

On the return trip of the General Ballou from Bremerhaven in December, 1948, Lt. J. L. Soelling continued the experimental study of seasickness. The following table (Table VI) is a record of the seasick passengers. The sex of the majority of these seasick passengers is female. Dramamine was prescribed to 73 passengers: 56 (77 per cent) were completely relieved in 24 hours, 9 (12 per cent) were completely relieved in 48 hours (a total of 89 per cent), 5 (7 per cent) were partially relieved, and 3 (4 per cent) of the group obtained no relief. To 36 seasick individuals, he gave a placebo. Sixteen (44 per cent) of this number recovered normal health after 24 hours, but 20 (56 per cent) of the group were worse than before the placebo had been prescribed. He then prescribed Dramamine to the 20 sick passengers. Fourteen (70 per cent) derived relief within one hour and 6 (30 per cent) derived partial relief in one hour.

The results of this supplementary report parallel those of the preliminary experiments.

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MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Hurd Hall, The Johns Hopkins Hospital, Monday, February 14, 1949

Dr. Harvey: The first paper on the program tonight is

MOTION SICKNESS—PREVENTION AND TREATMENT

by Drs. Leslie N. Gay and Paul E. Carliner. (This paper is published in full on page 470 of this issue of the Bulletin.)

Dr. Harvey: Dr. Gay and Dr. Carlinger's paper is open for discussion. Dr. Bard.

Dr. Bard: I am a little sick of seasickness myself. I would like to make one or two comments. Dr. Harvey. My contact with seasickness was during the war, as a member of an N.R.C. committee which was asked to find some information about it and, as Dr. Gay pointed out, the most effective preventive turned out to be hyoscine.

From a military point of view, prevention over relatively short periods of time in airborne and amphibious operations was the main problem, so tests were confined to relatively short periods of time—up to, let us say, twelve hours.

One thing that came from these studies was the great importance of methodology. One had always to take great care not to be fooled. Those of us who started in 1942 were often fooled and one of the chief sources of trouble was the statistical one; the question of whether, in a group of unselected personnel—about which you knew absolutely nothing of their past histories—you had within the group a sufficient number to provide the entire spectrum of susceptibility. Unless the percentage sick in the control group was pretty high, you have to have very large numbers, as our statistical studies showed.

As far as methodology was concerned, Dr. Gay referred to the matter of position, which is extremely important. He referred to Dr. Tyler's results, and I could refer him to others, which showed that as far as position of head is concerned one can reduce the incidence from somewhat in the neighborhood of 68 per cent to zero, simply by changing the angle of the head in relation to the motion of a swing by about forty degrees. So one wants to know whether these men of Dr. Gay's moved around; whether the treated men changed their positions more often than the untreated, who, for the most part, stayed flat on their backs, or flat on their stomachs, because they did not have the benefit of the treatment. And then one wonders whether that change in position added to the apparent effect of the drug.

It seems to me that the great contribution here is one of treatment of people already sick. I know of no evidence heretofore put forward which indicates that you could get anything like this result by giving the drug to very sick men. But I would like to point out that an incidence of 28 or 29 per cent in controls is not a high incidence. Hyoscine would certainly, on the basis of Dr. Tyler's work, have

protected nearly as many men as this drug, with the control incidence of only 28 per cent. To me, the outstanding feature of this work is the very marked effect on already sick men.

Dr. Harvey: Dr. Tyler, I didn't see you there. Would you like to make any comments?

Dr. Tyler: Well, I can appreciate fully the trials and tribulations that Dr. Gay must have gone through in running the experiment, particularly an experiment on an Army transport.

The results that have been presented here tonight are extremely interesting to me. In the first place, the indication that a medication other than hyoscine is effective in preventing motion sickness is indeed a real contribution. One thing I would surely like to see would be more tests, with a range of seasickness in the controls up to, say, 70 per cent. When you get an incidence of around 70 per cent you have adequate experimental conditions to assay the effectiveness of a proposed remedy.

There are one or two items that come into my mind that have no particular bearing on Dr. Gay's work. I am amazed by the Army's, and particularly the Surgeon General's, ignorance of some of the things that have been accomplished in regard to the problem of motion sickness. In the first place, there is the question of the side effects of hyoscine.

Now the administration of hyoscine in a dosage that is effective in preventing motion sickness—say up to six-tenths of a milligram—is surprisingly without any serious side effects on the combat efficiency of men as determined by a wide variety of tests. In fact, the Army could find in reports to the Surgeon General from the C M R that they have a very effective remedy that will prevent motion sickness in about 80 per cent of susceptibles when the incidence in the controls is 23 per cent. With an incidence of 60 per cent, one-half is protected. In addition to preventing motion sickness, a remedy available to the Army since 1938, one that contains hyoscine, also significantly improves the marksmanship of the average enlisted man.

I would like to emphasize what Dr. Bard pointed out here. We have never been able to find any remedy—barbiturates or hyoscine, or a combination of hyoscine and barbiturates—that could be used therapeutically (as distinct from prophylactically), and apparently we have such an agent now. That is indeed a real contribution to the problem.

Dr. Harvey: Is there any further discussion, or any questions anyone would like to ask?

Dr. Gay: I would like to make a few remarks at this time, if you don't mind before we leave the subject.

In the first place, of course, I don't like to argue with Dr. Tyler and Dr. Bard, as they are physiologists, but if there are any remedies that can be used for the treatment of seasickness they haven't appeared in the literature, to my knowledge, since 1942. Now, if I can take just a moment to point out some of the comments that were made by the men who were assigned to do seasickness studies in Eng-

land, Dr. Holling and his co-workers found that while hyoscine was effective, certainly they didn't recommend it for repeated doses in the control of seasickness. In their experiments they definitely said that "Chronic sufferers from seasickness"—I am quoting them—"may be astonished to learn that on most days through the year an obstinate and baffling calm haunts the waters around England." They commented that the waters were so calm in all of their studies they were not really able to try out their drugs in a very effective manner.

The same thing appeared in Dr. Best's article in which he, himself, said that attempts to make seasickness trials, using large numbers of subjects, were ruined by fair weather, and he said it is unlikely that a carefully controlled study at sea will be possible under peacetime conditions.

We feel that we have carried out a study under peacetime conditions and that it was very well controlled. Now, if we continue this study, and if we completely control seasickness so that no man on board ship, say 1,300 men, have seasickness, I can't see how statistics can be of much avail to say that the drug is not a good therapeutic agent from that point of view. We have had very few failures that we can say were real failures in the 311 men that were treated.

Dr. Harvey: Thank you very much, Dr. Gay.

The final paper tonight is on

TRANSFORMATION ON PNEUMOCOCCAL TYPES: A REVIEW

by Dr. Maclyn McCarty, of the Rockefeller Institute. Dr. McCarty will present a review of the work which has been done by himself and his associates at the Rockefeller Institute. (A similar review was published by Dr. McCarty in Bacteriological Reviews.) 1946, 10, 63.

It gives me great pleasure to introduce Dr. McCarty to you. He is a graduate from this School in 1937, and after three years of house service he went for a year's fellowship with Dr. Avery of New York. Since that time he has been at the Rockefeller Institute. Dr. McCarty.

Dr. Harvey: Dr. McCarty's paper is now open for discussion. Dr. Turner, do you have any comments to make?

Dr. Turner: Dr. Harvey, I am not qualified to discuss in detail Dr. McCarty's work, but I would like to point out some of the implications of the work which I think are very important indeed.

From the standpoint of the epidemiologist, we really do not know what causes an epidemic—whether it is a change in the host, or in the infecting organism. The preponderance of evidence, I might say, seems to be on the side of the change in the host; that is, herd immunity is built up and when that wanes epidemics occur. Yet that fails to explain striking seasonal correlations, so that the other theory assumes that a transformation of the parasite occurs.

Dr. McCarty's work has been done largely in vitro, but one wonders how often the same phenomenon may occur in nature.

We have one other striking example of a similar phenomenon: the Shope fibroma virus which produces a benign disease in rabbits, and the myxoma virus, which produces a very virulent disease. Combining heat inactivated myxoma virus with fibroma virus will impart to the latter the characteristics of the myxoma virus.

Another practical implication concerns the stability of immunological types. Are they as stable as we think?

Thirdly—I am taking off into thin air now—one of the current theories about the causation of cancer is the so-called transformation of the somatic cell. While work on the pneumococcus may be a long way removed from somatic cell mutation, the more we know about what causes cells to change their characteristics, perhaps the further along we shall be on that problem too.

Dr. Harvey. Are there any further questions or discussion of Dr. McCarty's paper?

Then the meeting is closed.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Blood Clotting and Allied Problems. Transactions of the First Conference, Josiah Macy, Jr. Foundation.

This publication is essentially a transcription of the informal discussions which took place at a conference sponsored by the Josiah Macy, Jr. Foundation in February 1948. The participants included many of the best known investigators in the field of blood clotting, representing several branches of medical science. Some of the recent developments in coagulation research are discussed in detail. Much space is devoted to description and discussion of various methods for determination of prothrombin. The authors are unable to agree upon a procedure for standardizing prothrombin assays although the need for such standardization is emphasized.

Those interested in blood coagulation should not fail to read this little volume. However, it is not in any sense a review of the subject, and the random manner of presentation will make reading difficult for those without particular interest in this field. The heated debate and vituperation which characterize some of the discussion add space to what is otherwise a very technical presentation.

C. L. C.

Blood Transfusion. By Elmer L. DeGowin, Robert C. Hardin, and John B. Alsever. W. B. Saunders Company, Philadelphia & London, 1949. 587 pages.

This is an attractively published little book, clearly and simply written. It is apparently designed as a fairly complete manual for laboratory technicians in blood banks and suits its purpose admirably. There are a few simple line drawings where required and no padding with unnecessary illustrations. The historical and scientific background of the various aspects of blood banking is simply and clearly given. The laboratory procedures themselves are given in great detail. This is by all odds the best conceived and most intelligently organized book which has yet been produced on the subject.

M. M. R.

Human Biochemistry. By Israel S. Kleiner. 2nd ed. C. V. Mosby Co., St. Louis, 1948.

Israel Kleiner, professor of biochemistry at the New York Medical College, in the preface to the first edition of his book, mentions the vital part played by biochemistry in medicine and its increasingly important role in diagnosis and therapeutics. Stated in this mild way, the author reflects the gradually enlarging appreciation of such values on the part of medical investigators, clinicians, and

biological scientists in many fields. He falls short of presenting the ringing challenge and needed dominance of such fundamental science in medicine and biology of the immediate future.

In the second edition, as in the first, the author attempts to present biochemistry in a more available form by not giving or discussing much of the evidence for the quite definitely stated material, and at the same time he attempts to include a large proportion of the subject-matter of biochemistry and some of its relation to medicine. The result to the reviewer's mind provides certain characteristics about the book which help to define its sphere of usefulness. These are that the contents form a fairly convenient reference for preliminary orientation on any subject; they also suggest some of the many relationships of biochemical conclusions to other fields. A person desiring a quick survey of a subject might turn to this book with advantage. He should do so, however, only with the realization that the brief statements given can be misleading (such as the effect of glutamic acid on brain function, page 339) and that a satisfactory understanding of the given subject can be acquired only by a study of the underlying evidence; for this he will have to look elsewhere. Professor Kleiner has not included many references, but those given should help to orient the student.

One interesting feature is the reference to clinical applications in a number of instances. However, these are relatively restricted in both number and scope, and the author does not attempt to correlate and unify the biochemical aspects of various disease states.

It should be realized that it is an almost impossible task to write a text-book in the fields of biochemistry and medicine that covers the ground and yet includes an adequate discussion of the evidence available on every subject, unless, perhaps, a new approach is made to the whole field. Professor Kleiner purposely has sacrificed a marshalling of the evidence and a more narrative style to put down as many of the conclusions on these subjects in as reasonable a space as he could. Subject-matter includes a good deal of recent work and the style is clear and readily followed.

F. W. B. Jr.

Surgical Treatment of the Abdomen. By F. W. Bancroft, and P. A. Wade. J. B. Lippincott Company, 1947. 460 Illustrations, $15.00.

This is an addition to the series of books on surgical treatment under editorial revision by the senior author. Abdominal diseases are discussed by thirty-six authors contributing twenty five chapters. This contributes to a lack of cohesion and an integrated point of view. Some chapters are written at the surgeon's level, others at the intern's or medical student's level. Of 990 pages, less than two-thirds are devoted strictly to abdominal surgery. The remaining third represents separate sections on anesthesia, diet, ward care and operating room behavior. Much of this additional material is covered in other texts or under other headings elsewhere in this book. One such extraneous chapter, however, is

a classic. By Mont Reid and Jean Stevenson, it discusses in peerless fashion details of surgical technique and the surgeon's conduct and the general philosophy of operating room treatment. This essay should be required yearly reading for every surgeon and aspirant. On a subject that could be platitudinous and pedestrian, it is fresh, glowing, inspiring. From this professional and literary height the sections vary all the way down to a treatise on diet that ascribes to intestinal putrefaction the blame for a large share of abdominal disease.

W. E. G.

BOOKS RECEIVED FOR REVIEW

Acclimatization in the Andes. By CARLOS MONGE. 130 pp., $2.75. *Published by The Johns Hopkins Press.*

Blood Transfusion. By ELMER L. DEGOWIN. 587 pp., 200 drawings, $9.00. *Published by W. B. Saunders Co., Philadelphia, Pa.*

Clinical Aspects and Treatment of Surgical Infections. By FRANK L. MELENEY. 840 pp., 287 figures, $12.00. *Published by W. B. Saunders Co., Philadelphia, Pa.*

1948 Facts about Nursing. 106 pp., 35 cents. *Published by American Nurses' Association, 1790 Broadway, New York.*

Mayo Clinic Diet Manual. By the Committee on Dietetics of the Mayo Clinic, 329 pp., $4.00. *Published by W. B. Saunders Co., Philadelphia, Pa.*

Tests and Measurements Applied to Nursing Education. By HYMAN KRAKOWER, PHD. 176 pp., $3.50. *Published by G. P. Putnam's Sons, New York City.*

The Business Side of Medical Practice. 2nd Edition. By THEODORE WIPRUD. 232 pp., 22 figures. *Published by W. B. Saunders Co., Phila., Pa.* $3.50.

Your Child or Mine: The Story of the Cerebral-Palsied Child. By MARY LOUISE HART BURTON in collaboration with SAGE HOLTER JENNINGS. 64 pp. $1.25. *Published by Coward-McCann, Inc. New York City.*